Türk Kadın Sağlığı ve Neonatoloji Dergisi

Turkish Journal of Women's Health and Neonatology e-ISSN: 2717-6622

Aralık 2024, Cilt:6 Sayı:4

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Turkish Journal of Women's Health and Neonatology

Publishing Services / Yayıncılık Hizmetleri

Akdema Bilişim Yayıncılık ve Dan. Tic. Ltd. Şti.
Kızılay Mah. Gazi Mustafa Kemal Bulvarı No: 23/8 06420 Çankaya/Ankara
E-posta: bilgi@akdema.com
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Türk Kadın Sağlığı ve Neonatoloji Dergisi
Eylül 2024, Cilt: 6, Sayı: 3 Üç Ayda Bir Yayımlanır
Makale gönderim adresi: https://dergipark.org.tr/tr/pub/etlikzubeyde

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Turkish Journal of Women's Health and Neonatology

Editorial / Editörden

Çok Değerli Okuyucularımız,

Türk Kadın Sağlığı ve Neonatoloji Dergisi (Turkish Journal of Women's Health and Neonatology) 2024 yılı dördüncü sayısıyla huzurlarınızdayız.

Bu sayımızda altı özgün araştırmayı zevkle okuyacağınızı ümit ediyoruz.

Serviks kanseri kadınlar arasındaki en ölümcül kanserlerden biridir ve gelişmekte olan ülkelerde sıklığını sürdürmektedir. Serviks kanseri, uzun süren, inatçı yüksek riskli insan papillomavirus (HPV) enfeksiyonu sonucu oluşmaktadır. HPV aşısı, HPV'ünün neden olduğu serviks kanseri ve genital siğilleri önlemeye yönelik uygulanan aşılardır. Bir çalışmada, İzmir'de kadın hastalıkları ve doğum ve pediatri asistanlarının HPV aşısı hakkındaki bilgi, tutum ve davranışlarını değerlendirilmiştir.

Meme kanseri, kadın nüfusunda kanserle ilişkili ölümün önde gelen nedenidir. Hiperlipideminin hipertansiyon, diyabet mellit ve kardiyovasküler hastalık gibi morbidite ve mortalite nedeni olduğu bilinmektedir. Bir çalışmada postmenopozal kadınlarda hiperlipideminin mamografi ile saptanabilen spesifik veya nonspesifik değişikliklere neden olup olmadığı araştırılmıştır.

Bir sonraki sayımızda yeni ve ilginç makalelerle buluşmak üzere…

Saygılarımla,
Prof. Dr. Yaprak Üstün
Baş Editör

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Turkish Journal of Women's Health and Neonatology

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Türk Kadın Sağlığı ve Neonatoloji Dergisi

To cite this article: Aydın N, Tüten N. Comparison of the effects of epidural analgesia and conventional analgesia on survival in patients undergoing gynecological oncological surgery : retrospective an analysis. Turk J Womens Health Neonatol 2024; 6(4): 111-118.

Original Article

Comparison of The Effects of Epidural Analgesia and Conventional Analgesia on Survival in Patients Undergoing Gynecological Oncological Surgery: A retrospective analysis

Jinekolojik Onkolojik Operasyon Geçiren Hastalarda Epidural Analjezi ile Geleneksel Analjezinin Sağkalım Üzerine Etkileri Karşılaştırılması: Retrospektif Bir Analiz

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Abstract

Purpose: We aimed to determine whether mortality due to gynecologic cancer differs in patients who received epidural analgesia versus conventional analgesia. Additionally, we aimed to investigate which analgesia approach results in a better prognosis for gynecologic cancer.

Materials and Methods: Patients who underwent surgery for a gynecologic malignancy were divided into two study groups based on the type of analgesia used: the Epidural Analgesia Group (n=120) and the Conventional Analgesia Group (n=88). All data were retrospectively collected from patient case charts. Variables recorded included patients' age, body mass index (BMI), presence of comorbid diseases, duration of anesthesia, amount of blood transfusion. During surgery, duration of hospital stay, duration of intensive care unit stay, presence of postoperative infection, and type of postoperative treatment.

Results: Survival after surgery tended to be higher in patients who received conventional analgesia (81 out of 88 patients) compared to those who received epidural analgesia (102 out of 120 patients), although this difference was not statistically significant (p=0.123). After controlling for all other factors, the coefficient for blood transfusion was -0.192 with a p- value of 0.007, indicating that a lower amount of blood transfusion was associated with increased survival. Similarly, the coefficient for the presence of comorbid diseases was -0.163 with a p-value of 0.022, suggesting that fewer comorbidities contributed to better survival post-surgery. Conventional analgesia showed higher survival rates (coefficient=0.163,p=0.022) compared to epidural analgesia. None of the other variables showed a significant correlation with survival.

Conclusion: This study is among the pioneering research efforts to explore the impact of analgesia methods on the prognosis of patients with non-metastatic gynecologic cancer. A lower amount of blood transfusion during surgery and fewer comorbid diseases contribute to improved survival rates.

Keywords: analgesia; epidural; prognosis

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ORCID: 0000-0003-0189-5865
DOI: 10.46969/EZH.1490197
Geliş tarihi: 28.05.2024 Kabul tarihi: 18.09.2024

Volume 6 Number 4 p: 111-118

Öz

Amaç: Epidural analjezi ve geleneksel analjezi uygulanan hastalarda jinekolojik kansere bağlı mortalitenin farklı olup olmadığını belirlemeyi ve ikinci olarak hangi analjezi yaklaşımının jinekolojik kanser prognozunda daha iyi olduğunu araştırmayı amaçladık.

Gereç ve Yöntem: Jinekolojik malignite nedeniyle ameliyat edilen hastalar kullanılan analjezi tipine göre iki çalışma grubuna ayrıldı: Epidural analjezi grubu (n=120) ve geleneksel analjezi grubu (n=88). Tüm veriler geriye dönük olarak hasta çizelgelerinden toplandı. Hastaların yaşı, vücut kitle indeksi (BKİ), ek hastalık varlığı, anestezi süresi, ameliyat sırasında yapılan kan transfüzyon miktarı, hastanede kalış süresi, yoğun bakımda kalış süresi, ameliyat sonrası enfeksiyon varlığı ve ameliyat sonrası tedavi şekli kaydedildi.

Bulgular: Cerrahi sonrası sağkalım geleneksel analjezi uygulanan hastalarda (88 hastanın 81'i), epidural analjeziye (120 hastanın 102'si) göre istatistiksel olarak fark olmaksızın daha yüksek olma eğilimindeydi (p=0.123). Diğer tüm faktörler kontrol edildikten sonra kan transfüzyonunun katsayısı -0,192 ve p değeri 0,007, komorbid hastalık varlığı katsayısı -0,163 ve p 0,022 değerine sahipti. Daha az miktarda kan transfüzyonu ve daha az eşlik eden hastalık, ameliyat sonrası hayatta kalma oranının artmasına katkıda bulunur. Geleneksel analjezi, epidural analjeziye göre daha yüksek sağkalım (katsayı=0,163, p=0,022) gösterdi. Diğer değişkenler hayatta kalma ile anlamlı bir korelasyon göstermedi.

Sonuç: Bu çalışma, analjezi yönteminin metastatik olmayan jinekolojik kanserli hastaların prognozuna etkisini araştıran önde gelen çalışmalardan biridir. Ameliyat sırasında daha az kan transfüzyonu yapılması ve eşlik eden hastalıkların daha az olması sağkalımın artmasına katkıda bulunur.

Anahtar Kelimeler: analjezi; epidural; prognoz

1. Introduction

Gynecologic cancers account for 12-15% of cancers in women (1). These cancers are most commonly diagnosed during the postmenopausal period, with 21% occurring during the reproductive period (1,2). Cervical cancer is more prevalent in sexually active women, whereas endometrial cancer is more frequent in sexually inactive women and during the postmenopausal period. Gynecologic cancers refer to malignant tumors originating from female genital organs. Among gynecologic cancers, cancers of the uterine corpus, cervix, and ovaries constitute the majority. According to American literature, cancers of the uterine corpus rank first (51%) among gynecologic malignancies, followed by ovarian cancer (26%) and cervical cancer (15%) (2). In European literature, cancers of the uterine corpus rank 6th among all cancers in women but remain the most common among gynecologic cancers. Worldwide, cervical cancer is the most frequent gynecologic cancer (3). According to data from Turkey, the estimated annual number of diagnosed cases is 844 for cervical cancer and 1477 for endometrial cancer (4).

The primary determinant of prognosis, recurrence, and survival is the surgical stage of the tumor. In addition to this, factors such as histological type, myometrial invasion, grade, patient age, genetic structure, concurrent tumors, and additional pathologies may affect prognosis (5). Several reports suggest that anesthetic methods may also influence prognosis (6-9). Although these findings are preliminary, several meta-analyses have supported this assertion. Regional anesthesia is believed to reduce surgery-induced stress and opioid use, leading many to argue that it lowers the risk of cancer recurrence (6).

We aimed to investigate whether mortality from gynecologic cancer differs between patients receiving conventional analgesia and those receiving epidural analgesia. Therefore, this retrospective study was conducted to determine which analgesic approach yields better prognosis for gynecologic cancer.

2. Methods

Study Design: The study was conducted in accordance with the principles of the Helsinki Declaration and approved by the local Institutional Review Board (KAEK No: 107, Date: 11/05/2022). Our study included patients who underwent gynecological oncological surgery in a single center at the tertiary level Kanuni Sultan Süleyman Training and Research Hospital between 2015 and 2017. Written informed consent was obtained from all subjects. This is a comparative study involving 208 patients who underwent surgery for gynecologic malignancy. Patients were divided into two study groups based on the type of analgesia used: Epidural analgesia group (EA Group) (n=120) and conventional analgesia group (CA Group) (n=88).

Patient Selection Criteria: Patients with American Society of Anesthesiologists (ASA) physical status I–III, aged between 20 and 80 years, and scheduled for gynecological oncological surgery were included in the study. Patients with coagulopathy,

drug allergies, ASA IV status, and those undergoing laparoscopic surgery were excluded.

Anesthesia and Analgesia Protocol: All patients received general anesthesia. An epidural catheter was placed at the lumbar 2-3 or 3-4 interspace before induction of general anesthesia. The position and function of the epidural catheters were confirmed with a test dose of 2-3 ml of 2% lidocaine.No complications developed in the patients who received epidural analgesia; only those whose epidural catheter did not work were excluded from the study.

General anesthesia induction was performed using the following medications: Dormicum 0.15 mg/kg (Midazolam, 50 mg/10 ml, Deva Holding, Istanbul, Turkey), Propofol 1.5–2 mg/kg (Propofol 200 mg/20 ml, Sandoz, Switzerland), Talinat 1–2 µg/kg (Fentanyl 0.5 mg/10 ml, Vem Pharmaceutical Industry, Istanbul, Turkey), and Esmeron 0.6 mg/kg (Rocuronium Bromide 50 mg/5 ml, Merck Sharp Dohme, USA). Maintenance of general anesthesia was continued with Sevorane (Sevoflurane, Abbott, Istanbul, Turkey), Ultiva (Remifentanil 2 mg, VLD Medical Products, Istanbul, Turkey), and a mixture of oxygen and air.

Patients in the conventional analgesia group received Contramal (Tramadol HCl 100 mg, Abdi Ibrahim, Istanbul, Turkey), Deksalgin (Dexketoprofen 50 mg/2 ml, Nobel, Istanbul, Turkey), and Parol (Paracetamol 10 mg/ml, Atabay, Istanbul, Turkey) 15 minutes before the end of general anesthesia. Patient-controlled epidural analgesia (PCEA) was initiated half an hour before the end of surgery. The PCEA protocol was as follows: Marcaine 0.5% 100 mg (Bupivacaine 5 mg/flacon, AstraZeneca, Kirklareli, Turkey) mixed with Talinat 200 micrograms in 100 ml of isotonic saline. The lockout interval was set at 30 minutes, and the infusion rate was 2 ml/hour. PCEA was continued for 3 days. Additional analgesics, such as opioids or paracetamol, were administered as needed.

Outcome Parameters: All data were retrospectively collected from patient case charts. Patient age, body mass index (BMI), presence of comorbid diseases, duration of anesthesia, amount of blood transfusion during surgery, duration of hospital stay, duration of intensive care unit stay, presence of postoperative infection, and type of postoperative treatment (chemotherapy vs. radiotherapy/brachytherapy) were recorded.

Statistical Analyses: Data were analyzed using IBM Statistical Package for Social Sciences v20 (SPSS Inc., Chicago, IL, USA). Normal distribution of quantitative data was assessed using the Kolmogorov-Smirnov test. Parametric tests were applied to normally distributed data, while non-parametric tests were used for data with questionable normal distribution. Independent-samples t-test and Mann-Whitney U-test were used to compare independent groups. Distribution of categorical variables in both groups was compared using the Pearson chi-square test. Partial correlation tests were used to calculate correlation coefficients. Logistic regression was performed to identify risk factors for overall survival. Data are presented as mean ± standard deviation (SD) or median (interquartile range), as appropriate. Statistical significance was defined as $p \leq 0.05$.

3. Results

Demographic Data: Demographic characteristics are presented in Table 1. No significant differences were observed between the groups except for anesthesia duration, amount of blood transfusion during surgery, and receipt of postoperative radiotherapy/brachytherapy treatment. Anesthesia duration was significantly longer in the epidural analgesia (EA) Group compared to the conventional analgesia (CA) Group (217.2 ± 83.9 vs. 168.5 ± 62.53 minutes, $p < 0.001$). The amount of blood transfusion during surgery was higher in the EA Group than in the CA Group, although this difference was not statistically significant ($p = 0.063$). A total of 26 patients in the EA Group and 9 patients in the CA Group received radiotherapy/brachytherapy treatment ($p = 0.029$).

Outcome: Survival assessment was performed for 3 years after the operation. Survival tended to be higher in patients who received conventional analgesia (81 out of 88 patients) compared to those who received epidural analgesia (102 out of 120 patients). Survival rates were 92.05% for conventional analgesia and 85% for epidural analgesia. However, there was no statistically significant difference ($p = 0.123$) (Table 2)

Logistic regression analysis for survival: All variables were included in logistic regression analysis for survival (Figure 1, Figure 2). The odds ratio for blood transfusion was 0.872 ($p = 0.044$). A lower amount of blood transfusion during surgery was identified as the primary factor contributing to increased survival following surgery (Table 3).

To accurately assess the relationship between two variables, we eliminated the influence of other variables using partial correlation analysis. Table 4 presents the results: after controlling for all other factors, blood transfusion had a coefficient of -0.192 and a p-value of 0.007, while the presence of comorbid diseases had a coefficient of -0.163 and a p-value of 0.022. A lower amount of blood transfusion and fewer comorbid diseases were found to contribute to increased survival following surgery.

Conventional analgesia showed higher survival (coefficient = 0.163, $p = 0.022$) compared to epidural analgesia. Other variables did not show a significant correlation with survival.

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Table 1. Demographic data				
		Epidural (n=120)	**Conventional (n=88)**	***p* Value**
Age (years) *mean±SD*		57.5±16.88	53.4±14.62	0.068
BMI (kg/m^2) *median (IQR)*		28.13 (4.1)	28.68 (5.2)	0.064
Comorbid diseases	Hypertension *(n)*	29	11	0.335
	Diabetes mellitus *(n)*	2	3	
	Congestive heart failure *(n)*	4	1	
	Asthma *(n)*	3	3	
Anesthesia time (minutes) *mean±SD*		217.2±83.9	168.5±62.53	<0.001
Hospital stay (days) *median (IQR)*		8.0 (7.0)	7.5 (5.0)	0.196
ICU: Intensive care unit stay (days) *median (IQR)*		0.0 (1.0)	0.0 (1.0)	0.639
Blood transfusion (units) median (IQR)		0.0 (4.0)	0.0 (2.0)	0.063
Postoperative infection	Wound site infection *(n)*	11	4	0.655
	Urinary tract infection *(n)*	2	2	
	Pulmonary infection *(n)*	7	4	
Postoperative treatment	Chemotherapy *(n)*	34	16	0.091
	Radiotherapy/Brachytherapy *(n)*	26	9	0.029
BMI: Body mass index; SD: Standard deviation; IQR: Interquartile range				

Table 2. Comparison of overall survival according to analgesia type			
	Epidural (n=120)	**Conventional (n=88)**	***p* Value**
Survival (n)	102	81	0.123
Dead (n)	18	7	
Total (n)	120	88	

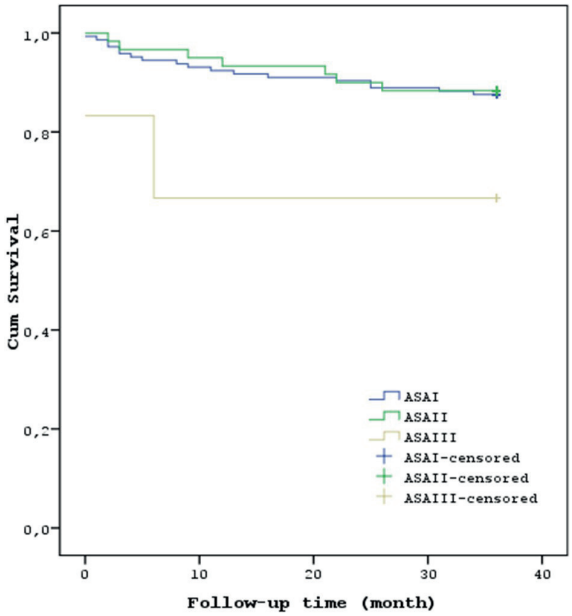

Figure 1. The ROC analysis for ASA score

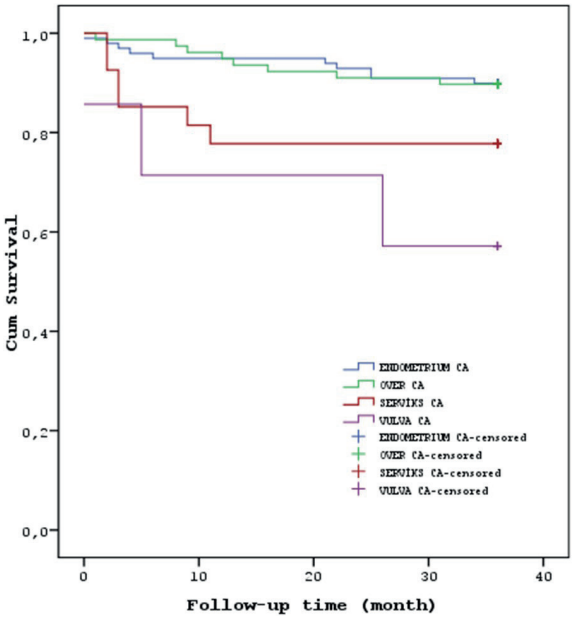

Figure 2. The ROC analysis for gynecological cancers

Table 3. Logistic regression analysis for overall survival			
		Odds ratio	***p* Value**
Age (years)		0.979	0.282
Weight (kg)		1.025	0.197
Height (cm)	Hypertension	0.966	0.251
Comorbid diseases	Diabetes mellitus	5.129	0.210
	Congestive heart failure	5.681	0.211
	Asthma	1.616	0.999
		3.848	0.439
Analgesia type (epidural / conventional)		0.759	0.638
Anesthesia time (minutes)		0.999	0.671
Hospital stay (days)		0.980	0.077
Intensive care unit stay (days)		0.845	0.409
Blood transfusion (units)		0.872	0.044
Postoperative infection	Wound site infection	1.083	0.937
	Urinary tract infection	0.668	0.723
	Pulmonary infection	5.190	0.999
Postoperative treatment	Chemotherapy	1.526	0.449
	Radiotherapy/Brachytherapy	1.516	0.496

Table 4. Partial correlation analysis with overall survival				
		Control variables	**coefficient**	***p* Value**
Age (yr)		All other variables	-0.030	0.680
Weight (kg)			-0.085	0.235
Height (cm)			-0.022	0.755
Comorbid diseases			-0.163	0.022
Analgesia type (epidural / conventional)			0.163	0.022
Anesthesia time (minutes)			-0.115	0.108
Hospital stay (days)			-0.134	0.060
Intensive care unit stay (days)			-0.077	0.279
Blood transfusion (units)			-0.192	0.007
Postoperative infection			-0.001	0.990
Postoperative treatment	Chemotherapy		0.114	0.109
	Radiotherapy/Brachytherapy		0.076	0.289

Diagnosis rates of patients: 46.9% Endometrial CA, 37.0% Ovarian CA, 12.8% Cervical CA, and 3.3% Vulvar CA. Epidural/ Traditional analgesia types: 51.5%/48.5% in patients with Endometrial CA, 60.3%/39.7% in patients with Ovarian CA, 70.4%/29.6% in patients with Cervical CA, and 57.1%/42.9% in patients with Vulvar CA. There was no statistically significant difference in analgesia types across diagnoses (p = 0.303) (Table 5).

Tablo 5. The relationship between cancer type and analgesia type							
Diagnosis	**Total**		**Type of analgesia**				
			Epidural		**Conventional**		
	n	**%**	**n**	**%**	**n**	**%**	**P**
Endometrial CA	99	46,9	51	51,5	48	48,5	0,303
Ovarian CA	78	37,0	47	60,3	31	39,7	
Cervical CA	27	12,8	19	70,4	8	29,6	
Vulvar CA	7	3,3	4	57,1	3	42,9	
Total	211	100	121	57,3	90	42,7	

Tablo 6. The relationship between cancer type and preoperative and postoperative hemoglobin values					
	PRE-OP HBG		**POST-OP HBG**		
	Mean ± SD	**Min-Max (Median)**	**Mean ± SD**	**Min-Max (Median)**	**P**
Total	11,5±1,9	6,9-16,5 (11,6)	10,6±1,6	7,2-16,4 (10,6)	<0,001
Diagnosis					
Endometrial CA	11,5±2,0	6,9-15,6 (11,9)	10,7±1,7	7,3-16,4 (10,9)	<0,001
Ovarian CA	11,6±1,9	7,7-16,5 (11,7)	10,6±1,5	7,2-14,1 (10,6)	<0,001
Cervical CA	10,9±2,0	7,4-14,6 (11,0)	10,2±1,6	7,3-14,6 (10,6)	0,011
Vulvar CA	12,1±1,4	10,5-14,1 (11,8)	10,8	8,5-12,5 (10,8)	0,063
p	0,369		0,424		

Tablo 7. Survival rate according to ASA score and the relationship between cancer type and mortality		
	3 year survival %(SE)	**Log Rank p**
Overall	87.2% (2.3	
ASA		
ASA I	87.6% (2.7%)	0.197
ASA II	88.3% (4.1%)	
ASA III	66.7% (19.2%)	
Cancer Type		
ENDOMETRIAL CA	89.9% (3%)	0.013
OVARIAN CA	89.7% (3.4%)	
CERVICAL CA	77.8% (8%)	
VULVAR CA	57.1% (18.7%)	

Tablo 8. The survival rate of gynecological cancers			
	ENDOMETRIAL CA	**OVARIAN CA**	**CERVICAL CA**
	Log Rank p	**Log Rank p**	**Log Rank p**
OVARIAN CA	0,975		
CERVICAL CA	0,076	0,089	
VULVAR CA	0,005	0,006	0,274

The decrease in post-operative hemoglobin levels in patients was found to be statistically significant ($p < 0.001$). Among the diagnoses, the decrease in hemoglobin levels was statistically significant in Endometrial CA ($p < 0.001$), Ovarian CA ($p < 0.001$), and Cervical CA ($p = 0.011$), but not statistically significant in Vulvar CA ($p = 0.063$). There was no statistically significant difference in preoperative and postoperative hemoglobin levels among diagnoses ($p = 0.369$, $p = 0.424$) (Table 6)

The survival rate according to ASA score and the relationship between cancer type and mortality are shown in Table 7. A statistically significant difference was found in survival rates across cancer types (p=0.013). The survival rate of vulvar CA was found to be lower than endometrial and ovarian CA (p=0.005 p=0.006) (Table 8).

4. Discussion

In the present study, we aimed to determine whether mortality due to gynecologic cancer differs in patients who received conventional versus epidural analgesia. We found that a lower amount of blood transfusion during surgery and fewer comorbid diseases contribute to increased survival. Furthermore, contrary to recent literature, we observed that conventional analgesia showed higher survival rates compared to epidural analgesia.

The relationship between surgery and anesthetic-induced immunosuppression and cancer recurrence remains unresolved. Surgery and anesthesia stimulate the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS), causing immunosuppression through several tumor-derived soluble factors. Local anesthetics such as lidocaine increase natural killer (NK) cell activity. Anesthetics such as propofol and locoregional anesthesia, which decrease surgery-induced neuroendocrine responses by suppressing the HPA axis and SNS, may result in less immunosuppression and lower recurrence rates for certain types of cancer compared to volatile anesthetics and opioids (10).

Perioperative anesthesia and analgesia exacerbate immunosuppression in immunocompromised cancer patients. NK cells are critical components of anti-tumor immunity. Propofol anesthesia combined with postoperative ketorolac analgesia demonstrated a favorable impact on immune function by preserving NK cell cytotoxicity (NKCC) compared to sevoflurane anesthesia and postoperative fentanyl analgesia in patients undergoing breast cancer surgery (11).

The effects of anesthesia in patients undergoing thyroid cancer surgery are still not well understood. Propofol anesthesia was associated with lower recurrence rates, but not mortality, following surgery for papillary thyroid carcinoma compared to desflurane anesthesia (12).

Many studies have been conducted on the association between cancer recurrence and general anesthesia. Cummings et al., in a large cohort study of 42,151 patients, reported that five-year survival is higher (adjusted hazard ratio = 0.91, $p < 0.001$) in patients who undergo epidural analgesia for colectomy (6). De Oliveira et al. concluded that epidural anesthesia for ovarian cancer surgery decreases the requirement for volatile agents and extends recurrence-free time (7). Lin et al. reported that epidural anesthesia during surgery and postoperative epidural analgesia decrease the mortality rate of ovarian serous adenocarcinoma (8). In that study, the general anesthesia group had a hazard ratio of 1.214 ($p = 0.043$) compared to the epidural group. Partial correlation tests showed that regional anesthesia increases 5-year survival.

In an experimental study on mice conducted by Wada et al., the authors suggested that spinal anesthesia with administration of sevoflurane is more effective in suppressing postoperative tumors and preventing infection. The interferon-gamma to IL-4 ratio demonstrated an increase in the spinal anesthesia group, and this increase in postoperative IL-4 was found to be statistically significant (13).

However, there are other reports which claim that regional anesthesia or analgesia has no effect on a cancer patient's prognosis. Hsiang-Ling Wu et al. did not find a significant association between epidural analgesia and risk of recurrence, all-cause mortality, or cancer-specific mortality in patients with rectal cancer undergoing tumour resection (14). Roiss et al. concluded that the oncological outcomes of 4,772 patients after radical prostatectomy were not affected by the adjunctive use of spinal anesthesia (15). A study by Chang WK et al did not support a definitive association between EA and cancer recurrence or overall survival (OS) after surgical resection in patients with primary hepatocellular carcinoma (HCC) (16).

In the present study, after controlling for all other factors, blood transfusion had a coefficient of -0.192 and a p-value of 0.007, while the presence of comorbid diseases had a coefficient of -0.163 and a p-value of 0.022. A lower amount of blood transfusion and fewer comorbid diseases contribute to increased survival following surgery. Conventional analgesia showed higher survival rates (coefficient = 0.163, $p = 0.022$) compared to epidural analgesia. Other variables showed no significant correlation with survival.

The limitations of our study include its retrospective design, small sample size, single-center study, unrecorded variables such as genetic profiles, and a smaller number of patients receiving conventional analgesia compared to those receiving epidural analgesia. Tumor staging is also critical factors that significantly influence the long-term prognosis of cancer patients.However, since the disease stages of the patients cannot be accessed in the pathology reports, the inability to evaluate the relationship between staging and survival is a limitation of our study.

5. Conclusion

This study is among the leading investigations into the effect of analgesia methods on the prognosis of patients with non-metastatic gynecologic cancer. Partial correlation analysis shows that a lower amount of blood transfusion during surgery and fewer comorbid diseases contribute to increased survival. Conventional analgesia demonstrated higher survival rates compared to epidural analgesia.

Author contribution

Study conception and design: NA and NT; data collection: NA and NT; analysis and interpretation of results: NA and NT; draft manuscript preparation: NA and NT. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the İstanbul S.B.U. Kanuni Sultan Süleyman Training and Research Hospital (Protocol no. 107/11.05.2022).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

Yazar katkısı

Araştırma fikri ve tasarımı: NA ve NT; veri toplama: NA ve NT; sonuçların analizi ve yorumlanması: NA ve NT; araştırma metnini hazırlama: NA ve NT. Tüm yazarlar araştırma sonuçlarını gözden geçirdi ve araştırmanın son halini onayladı.

Etik kurul onayı

Bu araştırma için İstanbul S.B.Ü. Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi Etik Kurulundan onay alınmıştır (Karar no: 107/11.05.2022).

Finansal destek

Yazarlar araştırma için finansal bir destek almadıklarını beyan etmiştir.

Çıkar çatışması

Yazarlar herhangi bir çıkar çatışması olmadığını beyan etmiştir.

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Türk Kadın Sağlığı ve Neonatoloji Dergisi

To cite this article: Tapkan C, Güngör T, Salman Özgü B. Assessment of insulin resistance, HOMA-IR, and QUICKI levels in patients with endometrial cancer and hyperplasia. Turk J Womens Health Neonatol 2024; 6(4): 119-123.

Orijinal Makale

Assessment of Insulin Resistance, HOMA-IR, and QUICKI Levels in Patients with Endometrial Cancer and Hyperplasia

Endometrium Kanseri ve Hiperplazisi Olan Hastalarda İnsülin Direnci, HOMA-IR ve QUICKI Düzeylerinin Değerlendirilmesi

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Abstract

Aim: To analyze insulin resistance and related parameters in patients with endometrial cancer and hyperplasia.

Methods: The study included 102 patients in 3 groups. Group I and II included patients with a histologic diagnosis of endometrial cancer (n=41, 40.2%) and endometrial hyperplasia (n=31, 30.4%) based on the final pathology report. Group III was the control group and included patients who had undergone surgery for a benign indication other than endometrial hyperplasia (n=30, 29.4%). Age, body mass index (BMI), menarcheal age, menopausal status, gravidity, parity score, diabetes, oral contraceptive status, fasting glucose levels, insulin levels, endometrial thickness, HOMA-IR and QUICKI scores were assessed.

Results: The mean age of group I was statistically higher than that of group II (55.3±9.5 vs. 48.8±7.1, p=0.002). The average BMI of the two groups was similar (p=0.076). When fasting glucose values were evaluated, group I showed significantly higher values compared to group II. The mean insulin and HOMA-IR values in the control group were significantly higher than those in group I (p<0.001) and the QUICKI value was significantly higher in group I than in the control group (p=0.026).

Conclusion: Insulin resistance appears to be associated with endometrial cancer.

Keywords: insulin resistance; endometrial cancer; hyperplasia

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Geliş tarihi: 04.08.2024 Kabul tarihi: 6.10.2024

Volume 6 Number 4 p: 119-123

Öz

Amaç: Endometriyal kanser ve hiperplazi hastalarında insülin direncini ve ilgili parametreleri analiz etmek.

Yöntemler: Çalışmaya 3 grupta 102 hasta dahil edildi. Grup I ve II, nihai patoloji raporuna göre histolojik tanısı endometriyal kanser (n=41, %40.2) ve endometriyal hiperplazi (n=31, %30.4) olan hastaları içermekteydi. Grup III kontrol grubuydu ve endometriyal hiperplazi dışında iyi huylu bir endikasyon nedeniyle ameliyat geçiren hastaları içeriyordu (n=30, %29,4). Yaş, vücut kitle indeksi (VKİ), menarş yaşı, menopoz durumu, gravidite, parite skoru, diyabet, oral kontraseptif durumu, açlık glukoz düzeyleri, insülin düzeyleri, endometriyal kalınlık, HOMA-IR ve QUICKI skorları değerlendirildi.

Bulgular: Grup I'in yaş ortalaması grup II'den istatistiksel olarak daha yüksekti (55.3±9.5 vs. 48.8±7.1, p=0.002). İki grubun VKİ ortalaması benzerdi (p=0.076). Açlık glukoz değerleri değerlendirildiğinde, grup I, grup II'ye kıyasla anlamlı derecede daha yüksek değerler göstermiştir. Kontrol grubundaki ortalama insülin ve HOMA-IR değerleri grup I'dekilerden anlamlı derecede yüksekti (p<0.001) ve QUICKI değeri grup I'de kontrol grubundan anlamlı derecede yüksekti (p=0.026).

Sonuç: İnsülin direnci endometriyal kanser ile ilişkili görünmektedir.

Anahtar Kelimeler: insülin direnci; endometrial kanser; hiperplazi

1. Introduction

Uninhibited estrogen forms the basis of the pathophysiology of endometrial cancer (EC), and any condition that leads to uncontrolled hyperestrogenism may play a role in the development of EC. However, metabolic abnormalities such as obesity, polycystic ovary syndrome (PCOS), type II diabetes, and components of the metabolic syndrome that lead to hyperestrogenism are often associated with insulin resistance (IR) and hyperinsulinemia (1-5). In addition, 33% of non-diabetic EC patients have IR, and hyperinsulinemia has also been shown to be associated with endometrial hyperplasia and endometrial proliferative disorders (6-9).

Elevated insulin plays a role in the pathogenesis of endometriosis in several ways. Via the endometrial cancer cell lines ECC-1 and USPC-1, it may play a direct role in stimulating cell proliferation and anti-apoptotic effects on the endometrium (7). In addition, elevated insulin levels can lead to cervical cancer due to increased insulin-like growth factor 1, decrease in sex hormone-binding globulin and inflammation, which can stimulate signaling pathways such as PI3K/Akt, Ras/MAPK and insulin-like growth factor receptor (8-10).

Based on this point of view, in this study we investigated hyperinsulinemia and insulin resistance in patients with endometrial hyperplasia and endometrial cancer compared to a control group using the very well accepted homeostasis model for assessing insulin resistance (HOMA-IR) and the quantitative index for testing insulin sensitivity (QUICKI) (11).

2. Materials and Methods

This study was conducted at Zekai Tahir Burak Women's Health Education and Research Hospital and was approved by the institutional review board of the hospital with the number (approval number:10). The study group included patients with endometrial cancer and endometrial hyperplasia compared to the control group, which included patients who had undergone hysterectomy for non-endometrial reasons. Over a period of five months (01.11.2014-01.04.2015), 102 patients were included in the study. All groups were informed about the study and voluntary informed consent was obtained. Our study was conducted in accordance with the latest principles of the Declaration of Helsinki. The study was designed as a retrospective case-control study.

All patients underwent hysterectomy and/or unilateral/bilateral salpingo-oophorectomy. However, patients who did not fulfill the Mayo criteria[12] underwent staging surgery (additional omentectomy and bilateral pelvic para-aortic lymphadenectomy).

The patients were divided into 3 groups: Group I and II included patients with a histologic diagnosis of endometrial carcinoma (n=41) and endometrial hyperplasia (n=31) based on the final pathology report. Group III was the control group and included patients who had undergone surgery for non-endometrial benign indications (n=30).

Age, age at menarche, menopausal status, body mass index (BMI (kg/m^2)), previous use of oral contraceptives, endometrial thickness (mm), fasting glucose level (mg/dL) were recorded. Fasting insulin and glucose levels were used to calculate the QUICKI value (1/(log(insulin))+ (log(plasma glucose(mg/dL)) and the HOMA value (insulin(mU/L)x(glucose (mmol/L)/22.5). There is no clear significance threshold for the detection of insulin resistance based on HOMA IR and QUICKI values. However, it is known that an increase in HOMA-IR and a decrease in QUICKI indicate insulin resistance.

Statistical analysis

The Statistical Package for Social Sciences (SPSS Inc, Chicago, IL) for Windows ® 22.0 was used to analyze the data. Pearson's chi-square test was used for categorical variables. The Kruskal-Wallis test was used to analyze three groups that were not normally distributed. Post-hoc analysis was performed using the Mann-Whitney U test after Bonferroni correction for the comparison of two groups. Logistic regression was also used to analyze the variables. The power analysis showed that the power for the difference in QUICKI score between patients with endometrial cancer or vice versa and patients with diagnosed or undiagnosed endometrial hyperplasia was 98.23% and 97.01%, respectively.

3. Results

A total of 102 patients were evaluated. Most patients with endometrial carcinoma had stage 1A (n=30, 73.2%) and grade 1 (n=22, 53.6%). Myometrial invasion > ½ was found in 10 (24.4%) patients and lymph node involvement in 5 (12.1%) patients. Among the patients with endometrial hyperplasia, 12 (38.7%) had complex atypical hyperplasia.

The mean age of the groups was 55.29±9.57, 48.84±7.06 and 54.77±8.75, respectively, and the difference between patients with endometrial cancer and patients with endometrial hyperplasia was statistically significant (p=0.002). When comparing the mean number of gravidities, the patients in the control group had significantly higher gravidities than those in group I (p=0.015). The mean BMI of the two groups was similar (p=0.076). The presence of postmenopausal status and diabetes was significantly more common in group I than in the other groups (p<0.001 and =0.017, respectively). The demographic data of the groups are shown in Table 1.

When fasting glucose values were evaluated, group I had significantly higher values compared to group II. The mean insulin and HOMA-IR values in the control group were significantly higher than those in group I (p<0.001) (Table 2).

4. Discussion

In our study, we investigated insulin resistance, HOMA-IR and QUICKI levels in patients with endometrial cancer and endometrial hyperplasia compared to a control group. Our results showed an association between endometrial cancer or hyperplasia and increased insulin resistance.

There are many risk factors for the development of endometrial cancer, but the exact cellular and molecular mechanism of carcinogenesis is still under investigation. Since EC is a hormone-dependent carcinoma, the risk increases with unbalanced estrogen levels and diseases that cause elevated estrogen levels (8).

Table 1. Demographic analysis of study groups

	Group I	Group II	Group III	P value
Age	55.29±9.57	48.84±7.06	54.77±8.75	0.002
Body Mass Index (BMI) (kg/m^2)	35.39±7.43	32.48±4,7	31.49±4.28	0.076
Menarche age	13.93±1.21	12.65±1.02	12.63±0.56	0.359
Gravida (n)	3±1	3±1	4±2	0.015
Parity	2±1	3±1	3±1	0.075
Menopause (patient n/%)	28/68.3%	7/22.6%	17/56.7%	<0.001
Diabetes (patient n/%)	18/43.9%	5/16.1%	6/20%	0.017
Using oral contraceptive history (patient n/%)	6/14.6%	7/22.6%	0	0.576

Table 2. Insulin, fasting glucose, HOMA-IR and QUICKI values between study groups

	Group I	Group II	Group III	P value
Fasting glucose level (mg/dL)	133.05±52.5	101.68±18.06	109.6±24.1	**0.002**
Insulin	8.1±12.2	8.73±11	19.46±16.4	**<0.001**
QUICKI (mg/dL)	0.35±0.14	0.34±0.13	0.32±0.05	**0.026**
HOMA-IR (µmol/L)	3.23±7.23	2.06±2.67	5.34±5.26	**<0.001**

The incidence of IR in the general population increases day by day with increasing obesity and is around 10-25% (11-19). Obesity and elevated insulin levels are associated with more severe endometrial pathology. However, weight loss increases insulin sensitivity and decreases mortality (19-20). Shan et al. have shown that BMI greater than 25 kg/m2 and menopausal status are risk factors for type 1 diabetes; in addition, abnormal metabolic changes have been demonstrated in the very early stages of endometrial hyperplasia (9). Type II diabetes and obesity are closely associated with an increased risk of EC (18). There are published data on decreased insulin response and increased fasting insulin levels, which are positively correlated with EC. In addition, hyperinsulinemia can also be found in non-obese women (11). Thus, hyperinsulinemia appears to be an independent risk factor for EC, in addition to non-opposed estrogen (17). There are published data on decreased insulin responsiveness and increased fasting insulin levels that positively correlate with EC, and hyperinsulinemia can also be found in non-obese women (11). In addition, fasting glucose levels was significantly higher in the endometrial cancer group than in the endometrial hyperplasia group and insulin resistance was more common in the endometrial cancer group.

Many different signaling pathways such as PI3K7Akt, Ras/MAPK and mediators such as insulin-like growth factor-1 (IGF-1) and sex hormone-binding globulin (SHBG) are involved in the complex mechanism of endometrial carcinogenesis through the action of insulin. Despite the role of insulin, the measurement of insulin resistance is quite difficult. Epidemiologic studies have produced some models such as HOMA-IR and QUICKI. However, it is not possible to establish a clear threshold for insulin resistance to establish a relationship with EC. HOMA-IR values are strong indicators of risk of EC, and they are significantly higher in patients with endometrial carcinoma (21). QUICKI assesses insulin sensitivity rather than insulin resistance and is the inverse of HOMA-IR. In a study by Burzawa et al. low QUICKI values were found in patients with endometrial cancer (<0.357) (10,21). Furthermore, it is clear that insulin resistance is higher in the endometrial cancer group (21-27).

The strengths of our study are the prospective structure, the selection of patients and the use of multiple methods to assess insulin resistance. The small number of cases was considered a limitation of the study.

In conclusion, we found a strong association between insulin resistance and endometrial cancer and hyperplasia in our study. Further studies on the severity of insulin resistance and endometrial disease will contribute to the literature.

Author contribution

Study conception and design: CT, TG; Data collection: CT, TG, BSO; analysis and interpretation of results: CT, TG, BSO; draft manuscript preparation: CT, TG, BSO. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ethics Committee for Noninterventional Studies of Zekai Tahir Burak Women's Health Education and Research Hospital (Approval date: 24/03/2014 Issue No.: 03/10).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

Yazar katkısı

Araştırma fikri ve tasarımı: CT, TG; veri toplama: CT, TG, BSÖ; sonuçların analizi ve yorumlanması: CT, TG, BSÖ; araştırma metnini hazırlama: CT, TG, BSÖ. Tüm yazarlar araştırma sonuçlarını gözden geçirdi ve araştırmanın son halini onayladı.

Etik kurul onayı

Bu araştırma için Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi Girişimsel Olmayan Çalışmalar Etik Kurulundan onay alınmıştır (Karar no: 24/03/2014, 03/10).

Finansal destek

Yazarlar araştırma için finansal bir destek almadıklarını beyan etmiştir.

Çıkar çatışması

Yazarlar herhangi bir çıkar çatışması olmadığını beyan etmiştir.

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Türk Kadın Sağlığı ve Neonatoloji Dergisi

To cite this article: Fıratlıgil FB, Savran Üçok B, Sağlam E, Akdaş Reis Y, Engin-Üstün Y. The influence of hyperlipidemia on the results of mammography in postmenopausal women. Turk J Womens Health Neonatol 2024; 6(4): 124-130.

Orijinal Makale

The Influence of Hyperlipidemia on the Results of Mammography in Postmenopausal Women

Postmenopozal Kadınlarda Hiperlipideminin Mamografi Sonuçları Üzerindeki Etkisi

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Abstract

Aim: To determine whether hyperlipidemia causes specific or nonspecific changes that can be detected by mammography in postmenopausal women.

Materials and Method: This study was conducted retrospectively and designed as a case-control study in the gynecology clinics of Etlik Zubeyde Hanim Women's Health Education and Training Hospital between January 2017 and January 2020. Healthy postmenopausal women with a total cholesterol (TC) level of 200 mg/dL and above 200 mg/dL, who were examined in our outpatient clinics and whose mammographic controls were performed in our hospital, were included in the study group (Group I). Healthy postmenopausal women with a TC level below 200 mg/dL who were followed up at the same clinic and whose mammographic controls were performed at our clinic were included in the control group (Group II). We analyzed TC, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides with mammography findings.

Results: There were no significant differences between the groups in terms of age and body mass index. There were no significant differences between smoking status and family history of breast cancer. The BAC and BI-RADS scoring category scores differed significantly (p=0.006 and p=0.042, respectively).

Conclusion: Postmenopausal women with hyperlipidemia have mammographic findings that can lead to breast cancer. Considering that hyperlipidemia may also have other causes of morbidity and mortality, such as hypertension, diabetes mellitus and cardiovascular disease, it is necessary to treat it with lifestyle changes and / or medications. As this was a retrospective study with a limited number of patients, it is clear that future randomized controlled trials could provide more reliable data on this topic.

Keywords: breast cancer; hyperlipidemia; mammography; post-menopause

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Geliş tarihi: 04.10.2024 Kabul tarihi: 06.10.2024

Öz

Amaç: Postmenopozal kadınlarda hiperlipideminin mamografi ile saptanabilen spesifik veya nonspesifik değişikliklere neden olup olmadığını belirlemek.

Gereç ve Yöntem: Bu çalışma Ocak 2017-Ocak 2020 tarihleri arasında Etlik Zübeyde Hanım Kadın Sağlığı Eğitim ve Araştırma Hastanesi jinekoloji kliniklerinde retrospektif olarak yürütülmüş ve vaka-kontrol çalışması olarak tasarlanmıştır. Polikliniklerimizde muayene olan ve mamografik kontrolleri hastanemizde gerçekleşen, total kolesterol (TC) düzeyi 200 mg/dL ve 200 mg/dL'nin üzerinde olan sağlıklı postmenopozal kadınlar çalışma grubuna (Grup I) dahil edildi. Aynı klinikte takip edilen ve mamografik kontrolleri kliniğimizde yapılan sağlıklı postmenopozal kadınlardan TC düzeyi 200 mg/dL'nin altında olanlar kontrol grubuna (Grup II) dahil edildi. Mamografi bulguları ile TC, düşük yoğunluklu lipoprotein kolesterol, çok düşük yoğunluklu lipoprotein kolesterol, yüksek yoğunluklu lipoprotein kolesterol ve trigliseridler analiz edildi.

Bulgular: Gruplar arasında yaş ve vücut kitle indeksi açısından anlamlı bir fark yoktu. Sigara içme durumu ve ailede meme kanseri öyküsü arasında anlamlı bir fark bulunmamıştır. BAC ve BI-RADS skorlama kategorileri değerleri arasında anlamlı fark vardı (sırasıyla p=0.006 vs p=0.042)

Sonuç: Hiperlipidemisi olan postmenopozal kadınlar meme kanserine yol açabilecek mamografik bulgulara sahiptir. Hiperlipideminin hipertansiyon, diabetes mellitus ve kardiyovasküler hastalık gibi başka morbidite ve mortalite nedenleri de olabileceği düşünüldüğünde, yaşam tarzı değişiklikleri ve/veya ilaç tedavisi ile tedavi edilmesi gerekmektedir. Bu çalışma sınırlı sayıda hastayı içeren retrospektif bir çalışma olduğundan, gelecekte yapılacak randomize kontrollü çalışmaların bu konuda daha güvenilir veriler sağlayabileceği açıktır.

Anahtar Kelimeler: meme kanseri; hiperlipidemi; mamografi; post-menopoz

1. Introduction

Breast cancer is one of the most commonly diagnosed malignancies worldwide and the leading cause of cancer-related death in the female population (1-4). Although it is more common in Western Europe and North America, more than 2 million new cases were detected in 2018 (2). Today, the prevalence is increasing in the older population and is more common in postmenopausal women (2,3). According to the American Cancer Society, the five-year survival rate has increased from 63% in 1960 to 90,8% today (5). This is thanks to early detection and improved treatment options through mammography screening, which has now become a routine examination in cancer prevention centers (2). The mortality rate has also fallen rapidly and was 6.6% in 2018 (2,5).

Several risk factors for breast cancer have been identified, which are referred to as modifiable and non-modifiable risk factors (6,7). Modifiable risk factors are important because they are preventable (8). These factors include dietary habits and obesity (8-10). Obesity in particular is associated with poor survival rates and increased mortality from breast cancer in postmenopausal women (9). Obesity is one of the biggest health problems in the world (11). The fact that most women in Turkiye are housewives, traditionally do not exercise and eat a diet high in carbohydrates and fat suggests that this could pave the way for obesity usually in the postmenopausal period and also pose a risk for breast cancer at this time (12). Some studies have also shown that a diet rich in foods containing fat and carbohydrates increases the risk of breast cancer (13). This increased risk explains why obesity in the postmenopausal period increases the risk of breast cancer (14).

Breast arterial calcification (BAC) is a radiologic finding on mammography that is not associated with cancer and usually occurs in postmenopausal women. BAC is classified as medial arterial calcification or Mönckeberg calcification, which is distinct from intimal calcification (15). Some studies suggest that BAC is associated with cardiovascular disease, diabetes or hypertension and can be used as a marker for arterial disease or cardiovascular disease (15,16). Arterial disease is associated with established risk factors for cardiovascular disease, including body mass index (BMI), elevated total cholesterol (TC) (≥ 200 mg/dL) (hyperlipidemia) or low-density lipoprotein cholesterol (LDL-C) levels, hypertension, and diabetes mellitus. BAC can be an indicator of arterial disease, cardiovascular disease and abnormal cardiovascular risk factors (16-18).

In light of this information, the aim of our study was to determine whether hyperlipidemia causes specific or nonspecific changes that can be detected by mammography in postmenopausal women.

2. Materials and method

This study was conducted retrospectively and designed as a case-control study in the gynecology clinics of Etlik Zubeyde Hanim Women's Health Education and Training Hospital between January 2017 and January 2020. This study was

conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee (with number: 01/08; January 2022).

Inclusion and exclusion criteria

Healthy postmenopausal women without underlying metabolic or systemic diseases (type 2 diabetes, high blood pressure, etc.) were included in the study.

Postmenopausal women were excluded from the study if they had any of the following risk factors or conditions: Hyperlipidemia due to secondary causes (including congenital adrenal hyperplasia, Cushing's syndrome, hyperprolactinemia, thyroid dysfunction, and adrenal disease); pre-existing systemic disease (hypertension, chronic renal failure, familial hypertriglyceridemia etc.); taking medication that affects carbohydrate or lipid metabolism (contraceptive pills, metformin, anti-epileptic drugs, antipsychotics, statins, and fish oil); women with known breast cancer or mammography changes; if BMI ≥ 40 kg/m2

Data

The sample size was calculated using a manual power analysis program. The analysis was calculated with an effect size of 0.20, an error of 0.05, and a power of 0.80. A total of 180 participants were identified. A sample of 90 cases (postmenopausal women with hyperlipidemia) and 90 controls (healthy postmenopausal women) was required for the study.

Data were extracted from patient records or hospital records of both groups, including demographic information (age, smoking status, family history of breast cancer), anthropometric parameters of the participants (height and weight to calculate body mass index), results of biochemical laboratory tests and mammography findings.

Study design

Healthy postmenopausal women with a TC level of 200 mg/dL and above 200 mg/dL, who were examined in our outpatient clinics and whose mammographic controls took place in our hospital, were included in the study group (Group I). Healthy postmenopausal women with a TC level below 200 mg/dL who were followed up in the same clinic and whose mammographic controls were performed in our clinic were included in the control group (Group II). We plan to form our control group by randomization from postmenopausal women who meet the inclusion criteria. We plan to perform the randomization in chronological order by including in the control group the postmenopausal women who were admitted to the outpatient clinic immediately after the women from the study group. We analyzed TC, LDL-C, very-low-density lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) with mammography findings.

Laboratory analysis of biological samples

We analyzed blood TC levels and other cholesterol components (LDL-C, HDL-C, TG and VLDL-C) using the ADVIA® 1800 Chemistry System (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA).

Statistical analyses

All statistical analyzes were performed using SPSS software (version 27.0, for Windows) was used to analyze the data (19). The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogrov-Simirnov/ Shapiro-Wilk's test) to determine whether or not they are normally distributed. Relationships between categorical variables were analyzed with the Chi-square test and relationships between non-categorical variables were analyzed with t-test. A p-value of less than 0.05 was considered to show a statistically significant result.

3. Results

After the data search, 238 postmenopausal women were found who had been admitted to our tertiary care hospital (Figure 1). After exclusion based on the criteria described in the Material and Methods section, 90 postmenopausal women who were admitted to our hospital between 2017 and 2020 with a high TC value for mammography control formed the study group (Group I) and 90 postmenopausal women who were included in the study according to the randomization system formed the control group (Group II).

A comparison of age, BMI and lipid profile is shown in Table I. There were no significant differences between the groups in terms of age and BMI (Table 1).

A comparison of BAC, Breast Imaging-Reporting and Data Systems (BI-RADS) scoring categories, smoking status and family history of breast cancer is shown in Table II. There were no significant differences between smoking status and family history of breast cancer. The BAC and BI-RADS scoring category scores differed significantly (p=0.006 and p=0.042, respectively) (Table 2).

4. Discussion

To our knowledge, there are few data that shed light on the effect of hyperlipidemia on mammography results in postmenopausal women. In this study, it was found that BAC and BI-RADS scoring categories were higher in postmenopausal patients with hyperlipidemia.

Table 1. Comparison of the groups in terms of age, BMI and blood lipid profiles

	Group I (n=90)					Group II (n=90)						
	Min.	Max.	X	SD	Median	Min.	Max.	X	SD	Median	t	p
Age (years)	45	78	60,61	6,90	60,00	48	76	58,64	6,93	57,00	1,908	0,058
BMI (kg/m^2)	19	40	28,67	4,15	29,00	22	36	27,74	2,69	28,00	1,768	0,079
TC	200	390	250,89	38,21	243,00	117	199	173,38	18,30	178,00	17,358	**0,000***
LDL-C	30	296	158,04	34,73	153,00	57	160	101,23	17,98	102,00	13,783	**0,000***
VLDL-C	10	75	29,58	13,96	26,00	9	32	19,36	5,33	19,00	6,489	**0,000***
HDL-C	36	107	60,98	13,63	62,00	33	160	52,83	13,71	54,00	3,997	**0,000***
TG	50	655	155,31	87,73	133,00	45	150	99,47	26,44	97,00	5,782	**0,000***

BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; n: numbers; SD: standart deviation; t: t-test; TC: total cholesterol; TG: triglycerides; VLDL-C: very-low-density lipoprotein cholesterol.
A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

Table 2. Comparison of the groups with regard to BI-RADS, calcification, smoking status and family history of breast cancer

		Group I (n=90)		Grup II (n=90)			
		n	%	n	%	X2	p
BI-RADS	0	4	4,4	0	0,0	8,226	**0,042***
	1	46	51,1	61	67,8		
	2	34	37,8	23	25,6		
	3-4	6	6,7	6	6,7		
BAC	No	44	48,9	62	68,9	7,435	**0,006***
	Yes	46	51,1	28	31,1		
Smoking status	No	74	82,2	82	91,1	3,077	0,079
	Yes	16	17,8	8	8,9		
Familial history of breast cancer	No	84	93,3	86	95,6	0,424	0,515
	Yes	6	6,7	4	4,4		

BAC: breast arterial calcification; BI-RADS: Breast Imaging-Reporting and Data Systems; n: numbers; X^2: chi square test.
A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

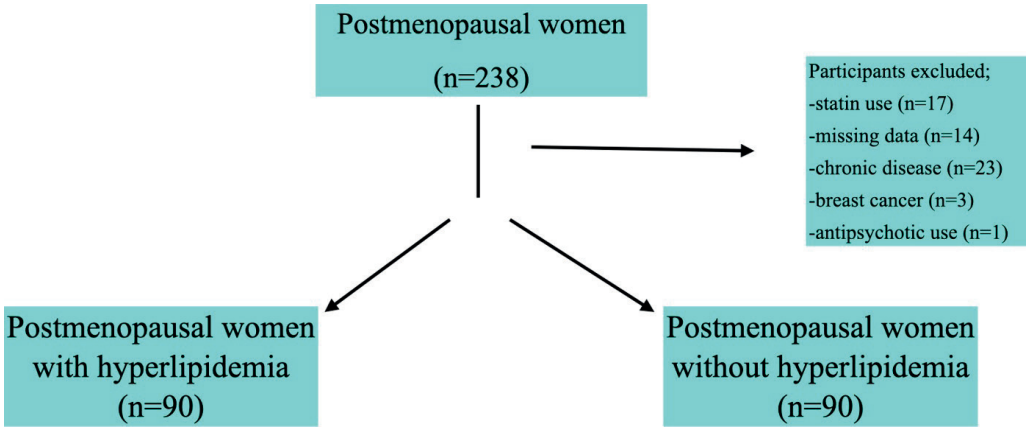

Figure 1. Flowchart of the participants

Hyperlipidemia is a term used to describe TC levels above the current threshold (TC ≥ 200 mg/dL) (20). Hyperlipidemia is a chronic and progressive but controllable disease whose treatment requires lifestyle and dietary changes and sometimes additional lipid-lowering medications (20). If hyperlipidemia remains uncontrolled, the disease progresses and can not only lead to severe arterial and cardiovascular disease, which is often fatal, but can also affect other tissues or organs (20,21). In a cross-sectional study by Torgutalp et al. (22), they concluded that patients with hyperlipidemia had significantly higher shear wave velocities in the patellar tendon and that hyperlipidemia had a direct effect on patellar tendon stiffness, independent of BMI. There is also a study showing that Achilles tendon damage occurs in patients with familial hypercholesterolemia due to cholesterol accumulation (23).

In Turkiye, women aged 40-69 years undergo mammography screening every two years in accordance with the National Standards of the Breast Cancer Screening Program for the early detection of breast cancer (24). In 1993, the American College of Radiology defined a scoring system for radiologists called BI-RADS to describe mammography findings (25). For each BI-RADS category, there is a corresponding follow-up plan to help physicians manage their patients appropriately (25). BI-RADS also contains four categories for breast density that can be specified so that the physician reading the mammogram can select the category that best describes the degree of breast density on the mammography (25). This is because dense breasts not only make mammograms difficult to read, but are also a risk factor for breast cancer (25). BAC is an identical finding in mammography that was first described by Sickles et al. in 1985 (26). It was later described by Cetin et al. (27) as calcium deposition in the medial layer of peripheral arterioles and termed Mönckeberg medial calcified sclerosis or medial arterial calcification on the mammogram. Studies have been published showing an association between BAC and cardiovascular disease, hypertension and diabetes mellitus (28).

In this study, we also attempted to demonstrate the association between mammography findings and hyperlipidemia. In a study conducted by Caglayan et al. (29) comparing breast density and hyperlipidemia in 215 postmenopausal women, no statistically significant difference was found between the groups of 40 women with dense breast tissue and 175 women with non-dense breast tissue. Kim et al. (30) identified age, height, weight, BMI, hematocrit, mean corpuscular hemoglobin, red blood cell distribution width, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, uric acid, gamma-glutamyl transferase, TG, TC, HDL-C and LDL-C as factors that may influence breast density. In our study, postmenopausal women with hyperlipidemia were found to have significant differences in BAC and BI-RADS scoring categories on mammography, independent of age, smoking, BMI and family history of breast cancer. From our results it can be concluded that BAC and BI-RADS are increased in postmenopausal women with hyperlipidemia, which in turn increases the risk of breast cancer.

In conclusion, postmenopausal women with hyperlipidemia have mammographic findings that can lead to breast cancer. Considering that hyperlipidemia may also have other causes of morbidity and mortality, such as hypertension, diabetes mellitus and cardiovascular disease, it is necessary to treat it with lifestyle changes and / or medications. As this was a retrospective study with a limited number of patients, it is clear that future randomized controlled trials could provide more reliable data on this topic.

The strengths and limitations

The study was conducted as a retrospective case-control study, so it has some limitations due to its design. This is because we lacked some data/information from the participants and the number of participants was small. The strength of the study depends in the fact that it was conducted in a large tertiary referral center, where the same algorithms were used to follow up the patients and the groups were conducted with G-power analyzes.

Author contribution

Study conception and design: FBF, BSÜ, and YAR; data collection: FBF, BSÜ, and YAR; analysis and interpretation of results: ES; draft manuscript preparation: FBF, ES, and YEÜ. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Etlik Zubeyde Hanim Women's Health Education and Research Hospital (Protocol no. 01/11.01.2022).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

Yazar katkısı

Araştırma fikri ve tasarımı: FBF, BSÜ ve YAR; veri toplama: FBF, BSÜ ve YAR; sonuçların analizi ve yorumlanması: ES; araştırma

metnini hazırlama: FBF, ES ve YEÜ. Tüm yazarlar araştırma sonuçlarını gözden geçirdi ve araştırmanın son halini onayladı.

Etik kurul onayı

Bu araştırma için Etlik Zübeyde Hanım Kadın Hastalıkları Eğitim ve Araştırma Hastanesi Etik Kurulundan onay alınmıştır (Karar no: 01/11.01.2022).

Finansal destek

Yazarlar araştırma için finansal bir destek almadıklarını beyan etmiştir.

Çıkar çatışması

Yazarlar herhangi bir çıkar çatışması olmadığını beyan etmiştir.

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Türk Kadın Sağlığı ve Neonatoloji Dergisi

To cite this article: Şahin B, Yaman E, Düzenli FN, Davran F. The role of inflammatory markers in distinguishing endometrial polyp: Single center results. Turk J Womens Health Neonatol 2024; 6(4): 131-136.

Orijinal Makale

The Role of Inflammatory Markers in Distinguishing Endometrial Polyp: Single Center Results

Endometrial Polipi Ayırt Etmede İnflamatuar Belirteçlerin Rolü: Tek Merkez Sonuçları

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Abstract

Objective: To investigate the role of inflammatory markers in predicting the presence of endometrial polyps in patients undergoing endometrial sampling due to abnormal uterine bleeding.

Methods: The pathology results of patients who presented to Akçakoca State Hospital with abnormal uterine bleeding and underwent endometrial sampling between May 2023 and July 2023 were retrospectively examined. The demographic characteristics of the patients, platelet-lymphocyte, neutrophil-lymphocyte and lymphocyte-monocyte ratios and systemic immune inflammation index were calculated. Patients were categorized into endometrial polyps and other benign pathologies according to the pathological diagnosis. Malignant and premalignant lesions were not included in the study. The examination results and inflammatory markers were compared between these two groups.

Results: 89 patients were included in the study. While the pathological finding in 38 patients was an endometrial polyp, other benign pathologies were found in 51 patients. No significant difference was found in terms of hemoglobin, hematocrit, lymphocytes, monocytes, platelets, neutrophils and PDW variables in patients with endometrial polyps ($p>0.05$). PLR (platelet-to-lymphocyte ratio) and SII (systemic immune-inflammatory index) were significantly higher in the endometrial polyp group compared to other benign pathologies ($p<0.05$). NLR (neutrophil to lymphocyte ratio) was higher in the endometrial polyp group and was not significant (p: 0.056). SII was 669884.4±410641.7 in the endometrial polyp group and was higher than other benign pathologies. ($p<0.05$)

Conclusion: Endometrial polyps are one of the most important causes of abnormal uterine bleeding. NLR, PLR and SII are parameters of the systemic immune response that can be easily determined with blood tests at no additional cost. SII appears to be an effective and simple test to differentiate endometrial polyps from benign endometrial pathologies.

Keywords: abnormal uterine bleeding; endometrial polyps; Systemic immune-inflammatory index

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DOI: 10.46969/EZH.1538701
Geliş tarihi: 04.09.2024 Kabul tarihi: 16.10.2024

Volume 6 Number 4 p: 131-136

Öz

Amaç: Anormal uterin kanama nedeniyle endometrial örnekleme yapılan hastalarda endometrial polip varlığını öngörmede inflamatuar belirteçlerin rolünü değerlendirmek.

Yöntem: Mayıs 2023- Temmuz 2023 tarihleri arasında Akçakoca Devlet Hastanesine anormal uterin kanama ile başvuran ve endometriyal örnekleme yapılan hastaların patoloji sonuçları retrospektif olarak tarandı. Hastaların demografik özellikleri, Trombosit-lenfosit, nötrofil-lenfosit ve lenfosit-monosit oranları, sistemik immün inflamasyon indeksi hesaplandı. Hastalar patolojik tanıya göre endometrial polip ve diğer bening patolojiler olmak üzere gruplandırıldı. Malign ve premalign lezyonlar çalışmaya dahil edilmedi. Tetkik sonuçları ve inflamatuar belirteçler bu iki grup arasında karşılaştırıldı.

Bulgular: Çalışmaya 89 hasta dahil edildi. 38 hastanın patoloji sonucu endometrial polip iken 51 hastada diğer bening patolojiler saptandı. Endometrial polip olan hastalarda hemoglobin, hemotokrit, lenfosit, monosit, platelet, nötrofil ve PDW değişkenleri açısından anlamlı bir fark saptanmadı (p>0,05). PLR (trombosit-lenfosit oranı) ve SII (sistemik immün-inflamatuar indeks) endometial polip grubunda diğer bening patolojilere göre anlamlı olarak daha yüksek bulundu (p<0,05). NLR (nötrofil-lenfosit oranı) endometrial polip grubunda daha yüksek olup anlamlı değildi (p: 0,056). SII endometrial polip grubunda 669884,4±410641,7 olup diğer bening patolojilere göre daha yüksekti (p<0,05).

Sonuç: Endometrial polip anormal uterin kanamanın önemli sebeplerinden biridir. NLR, PLR ve SII ek bir maliyet gerektirmeksizin kan testleri ile kolayca değerlendirilebilen sistemik immün yanıt parametreleridir. SII bening endometrial patolojiler arasında endometrial polipi ayırt etmede etkili ve basit bir tetkik olarak görünmektedir.

Anahtar Kelimeler: anormal uterin kanama; endometrial polip; sistemik immün-inflamatuar indeks

1. Introduction

Abnormal uterine bleeding is defined as bleeding that is outside the 5th to 95th percentile of the general population in terms of frequency, duration, regularity and amount of menstrual bleeding, with pregnancy excluded. Menstrual cycles that are shorter than 24 days or longer than 38 days, a difference of more than 9 days between menstrual cycles, cycles that last longer than 8 days, blood loss greater than 80ml, and intermenstrual bleeding are all indicative of abnormal uterine bleeding (1).

Endometrial polyps (EP) are one of the most common causes of abnormal uterine bleeding in both premenopausal and postmenopausal patients. They are defined as benign growths of the endometrial glands and stroma (2,3). Factors such as monoclonal endometrial hyperplasia, overexpression of endometrial aromatase, somatic gene mutations, cytogenetic restructuring, etc. are thought to be responsible for the pathogenesis (4-9). Although the actual incidence is unknown due to asymptomatic cases, it is observed with an incidence between 7.8% and 50%. It is mostly benign and 1-3% malignant transformation can be expected in postmenopausal patients. Recent studies have shown a strong correlation between endometrial polyps and a disturbed inflammatory status of the endometrium (10-16).

There are studies showing that the expression of transforming growth factor alpha-1 (TGF-α1) and vascular endothelial growth factor (VEGF), which are proinflammatory markers that are elevated in chronic inflammatory diseases, is also increased in EPs (3,14,17). In addition, risk factors related to chronic inflammation are among the EP risk factors. Studies showing that gynecologic malignancies, especially pathologies of the cervix and endometrium, are associated with chronic inflammation show us that inflammatory processes may also play a role in the development of endometrial polyps (18-20).

The Systemic Inflammatory Immune Index (SII) is a novel biomarker that reflects the immune response and systemic inflammation. Peripheral blood cell-derived inflammatory indices (NLR, PLR, NML, LMR) have recently attracted much attention and have been studied for many diseases as they are easily measurable and accessible. They have been shown to be a prognostic factor in many different clinical conditions, including coronary heart disease, inflammatory diseases, solid organ tumors, obstetric and gynecologic diseases, endometrial hyperplasia, and endometrial cancer. Our aim in this study was to evaluate the role of inflammatory markers in the prediction of endometrial polyps associated with impaired endometrial inflammatory status.

2. Material and Methods

The study protocol was approved by the Ethics Committee of Duzce Unıversity (19/08/2024, #2024/153), and the principles of the Declaration of Helsinki were followed.

For our retrospective cross-sectional observational study, patients who presented with abnormal uterine bleeding to the hospital's gynecology and obstetrics outpatient

clinic and underwent endometrial sampling between May 2023 and July 2023 were recorded via the medical record. Patients with premalignant and malignant lesions on pathology, postmenopausal and obese patients, patients with inflammatory diseases and patients with a history of malignancy were excluded. Demographic characteristics, obstetric and reproductive history, comorbidities, complete blood count and pathology results obtained prior to endometrial biopsy were evaluated. The complete blood count parameters (hemoglobin, hematocrit, platelets, lymphocytes, neutrophils, neutrophils, monocytes, hemoglobin, platelets, lymphocytes, neutrophils, monocytes) obtained from the patients before the procedure were analyzed using the PDW Sysmex CA-600 device. PLR (platelets/lymphocytes), NLR (neutrophils/lymphocytes), NMR (neutrophils/monocytes), LMR (lymphocytes/monocytes) and SII (neutrophils x platelets/lymphocytes) were calculated for the assessment of inflammatory indices and the values were recorded on the patient's follow-up form. The patients were divided into two groups according to the results of the benign pathology: Endometrial polyps and non-endometrial polyps (proliferative endometrium, secretory endometrium, atrophic endometrium, etc.).

Statistical analysis

Statistical Package for the Social Sciences -SPSS 22 (SPSS Inc, Chicago, IL) was used for the statistical analysis. The distribution of parameters was tested using the Shapira-Wilk normality test. Data were expressed as mean ± standard deviation and median (min-max). The t-test for independent samples was used for the normally distributed data and the Mann Whitney U-test for the non-normally distributed variables. The, chi-square test or Fisher's exact test was used.to analyse the categorical variables. A total type I error level of 5% was used to derive statistical significance.

3. Results

The study population comprised 89 patients who met the pre-established inclusion and exclusion criteria. Histopathology revealed the presence of endometrial polyps in 42% of patients, while 58% exhibited other benign histopathologic findings. Upon analysis of the reproductive characteristics of the patients, no statistically significant difference was observed between the groups in terms of gravida, parity, and abortion history ($p > 0.05$). The mean age of the patients was comparable between the two groups (Table 1). The mean age was 43.5±6.6 years in patients with endometrial polyps and 45.2±7.0 years in patients without endometrial polyps (p=0.278). Upon individual analysis of complete blood count parameters, it was observed that patients with EP exhibited a mean haemoglobin value of 11.9±1.5, which was found to be lower than that of the group without endometrial polyps. Nevertheless, no statistically significant difference was identified between the two groups ($p = 0.335$). The values for lymphocytes, monocytes, thrombocytes and neutrophils were found to be similar between the groups ($p > 0.05$). Upon analysis of the inflammatory indices, it was determined that the PLR was markedly elevated in the EP group. The PLR value was 151.2 ± 56.9 in the EP group and 128.7 ± 39.5 in the group without coexisting endometrial polyp. The NLR value was 2.4±1.8 in the EP group, indicating a higher level than that observed in the group without endometrial polyps (p=0.056). The systemic inflammatory immune index was calculated to be 669884.4±410641.7 in the EP group, exhibiting a significantly higher value in the EP group (p=0.022) compared to the group without endometrial polyps (Table 2).

4. Discussion

Recent studies have shown a strong correlation between endometrial polyps and a disturbed inflammatory status of the endometrium. In our study, we found that inflammatory indices were higher in patients with endometrial polyps than in patients without EP, with SII and PLR being statistically significant. Our results show that inflammatory status has an impact on the formation of endometrial polyps.

In the literature, the relationship between inflammatory indices and malignant and premalignant endometrial pathologies has been investigated in studies on inflammatory indices. The fact that chronic inflammation is associated with tissue damage and cellular changes that can lead to proliferation and mutations suggests that inflammation has an important influence on carcinogenesis (21,22). The inflammation associated with

Table 1. Comparison of complete blood count parameters between patients with and without coexisting endometrial polyp

	EP N: 38	No EP N:51	p
Age (years)	43,5±6,6	45,2±7,0	0,278
Hemoglobin (g/dl)	11,9±1,5	14,1±14,1	0,335
Hematocrit (%)	36,5±3,7	37,2±3,3	0,326
Lymphocyte (ml)	2083±770	2300±874	0,228
Monocyte (ml)	527±220	549±154	0,587
Platelet (ml)	288789±79535	274470±70848	0,373
Neutrophil (ml)	4403±1730	4056±1178	0,264
PDW (fl)	11,6±1,8	12,0±2,1	0,414

*Data are given as mean ± Standard Deviation (SD).
EP: Endometrial Polyps. No EP: without coexisting endometrial polyp

Table 2. Comparison of inflammation indices between patients with and without coexisting endometrial polyp			
	EP N: 38	No EP N:51	p
Mean platelet volüme (fl)	10,1±0,8	10,3±0,9	0,409
Platelet to lymphocyte ratio (PLR)	151,2±56,9	128,7±39,5	**0,030**
Neutrophil to lymphocyte ratio (NLR)	2,4±1,8	1,8±0,6	**0,056**
Neutrophil to monocyte ratio (NMR)	11,7±20,4	7,7±2,8	0,176
Lymphocyte to monocyte ratio (LMR)	4,2±1,6	4,2±1,2	0,947
SII	669884,4±410641,7	516280,5±196718,7	**0,022**
**Data are given as mean ± Standard Deviation (SD). EP: Endometrial Polyps, No EP: without coexisting endometrial polyp, SII: Systemic immune-inflammatory index			

carcinogenesis occurs mainly in the systemic circulation and in the tumor microenvironment and manifests as neutrophilia, thrombocytosis and lymphocytopenia in the peripheral blood (23). Based on this biological behavior of the tumor and its consequences in the peripheral blood, inflammatory indices have been developed to reflect the inflammatory status in the presence of malignant disease (24). In the study conducted by Cakmak et al., higher NLR and PLR values were found in patients with atypia-hyperplasia than in patients without atypia-hyperplasia and non-hyperplasia (25). Another study reported that SII is an independent risk factor for lymph node metastasis and myometrial invasion in patients with endometrial cancer (26). In a study by Gökulu et al. on the effect of SII on endometrial pathologies, the role of inflammatory indices in predicting endometrial cancer in the presence of atypia-hyperplasia was investigated, but no significant difference was found between the groups. This result was attributed to the fact that the patients had early adenocarcinoma (27). All these studies show the importance of inflammatory status in malignant endometrial pathologies. And they show the impact of a disturbed inflammatory status of the endometrium on the development of malignancy.

The review by Drizi et al. emphasizes the concept of impaired inflammatory status of the endometrium (IISE) and mentions that inflammatory processes have an impact on the pathogenesis of endometrial pathologies, including benign pathologies, and that treatment of IISE with the right anti-inflammatory therapies is important to prevent future pathologies. The elevation of VEGF, TGF alpha 1 (proinflammatory) in patients with endometrial polyps, the presence of risk factors associated with chronic inflammation in EP patients, the barrier effect of the inflammatory state on sperm transport and implantation in EP, and the increase in pregnancy rates after resection, the presence of chronic inflammation in the background of cervical and endometrial malignancies show that the impaired inflammatory state of the endometrium is the cause of many pathologies (28).

In our study, we found that the SII was effective in predicting endometrial polyps, a benign pathology. While the inflammatory indices (PLR, NLR, NMR, SII) were higher in the patient group with endometrial polyps, only SII and PLR were statistically significant. The fact that the study was conducted in a single center and with the same team is one of the strengths of the study. It is the first study to investigate the relationship between endometrial polyps and inflammatory indices. Limitations of the study include the retrospective study design and the limited number of patients. Further studies are needed to uncover the rwlationship between endometrial pathologies and an impaired inflammatory status of the endometrium especially in endometrial pathologies.

Author contribution

Study conception and design: BŞ; data collection: BŞ, EY, and FND; analysis and interpretation of results: BŞ and FD; draft manuscript preparation: BŞ, FND, and EY. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Duzce University (Protocol no. 2024/153/19.08.2024).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

Yazar katkısı

Araştırma fikri ve tasarımı: BŞ; veri toplama: BŞ, EY ve FND; sonuçların analizi ve yorumlanması: BŞ ve FD; araştırma metnini hazırlama: BŞ, FND ve EY. Tüm yazarlar araştırma sonuçlarını gözden geçirdi ve araştırmanın son halini onayladı.

Etik kurul onayı
Bu araştırma için Düzce Üniversitesi Etik Kurulundan onay alınmıştır (Karar no: 2024/153/19.08.2024).

Finansal destek
Yazarlar araştırma için finansal bir destek almadıklarını beyan etmiştir.

Çıkar çatışması
Yazarlar herhangi bir çıkar çatışması olmadığını beyan etmiştir.

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Türk Kadın Sağlığı ve Neonatoloji Dergisi

To cite this article: Ermiş N, Onur D, Er A, Günay İ. Evaluation of knowledge, attitudes, and practices about HPV vaccine: A survey study of pediatric and obstetrics and gynecology residents in İzmir, Türkiye. Turk J Womens Health Neonatol 2024; 6(4): 137-146.

Orijinal Makale

Evaluation of Knowledge, Attitudes, and Practices About HPV Vaccine: A Survey Study of Pediatric and Obstetrics and Gynecology Residents in İzmir, Türkiye

HPV Aşısı Hakkında Bilgi, Tutum ve Davranışların Değerlendirilmesi: İzmir'de Pediatri ve Kadın Hastalıkları ve Doğum Asistanları Arasında Bir Anket Çalışması

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Abstract

Purpose: The main objective of this study was to evaluate the knowledge, attitudes, and practices of obstetrics and gynecology (OB/GYN) and pediatric residents in Izmir, Turkey, regarding the HPV vaccination.

Materials and Methods: This cross-sectional survey study was conducted in five hospitals in Izmir, Turkey, between May and July 2019. The data for this study were obtained from 299 pediatric and 126 OB/GYN residents via an online web-based questionnaire. The statistical analyses were performed using SPSS®.

Results: The overall participation rate was 72%. Only 25.2% of the participating residents demonstrated adequate knowledge about the HPV vaccine. The OB/GYN residents had significantly higher knowledge scores than the pediatric residents (median [IQR] = 9.4 [8.4-10.6] vs. 8.4 [7.4-9.8], p=0.007). The vaccination rate among residents was low, with female residents having higher rates of vaccination than male residents (13.6% vs. 1.1%, p<0.01). While 68.3% of residents indicated that they would vaccinate both their sons and daughters, only 13.1% always recommended the HPV vaccine to their patients.

Conclusion: This study revealed that the knowledge and vaccination rates of OB/GYN and pediatric residents regarding the HPV vaccine are insufficient. Enhancing education and support for these physician groups is crucial for improving HPV vaccination rates and reducing the prevalence of HPV-related diseases in the population.

Keywords: HPV vaccines; pediatrics; gynecologist; residency; health knowledge; attitudes; practice

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DOI: 10.46969/EZH.1555150
Geliş tarihi: 24.09.2024 Kabul tarihi: 16.10.2024

Volume 6 Number 4 p: 137-146

Öz

Amaç: Bu çalışmanın birincil amacı, İzmir, Türkiye'deki Kadın Hastalıkları ve Doğum (OB/GYN) ve pediatri asistanlarının HPV aşısı hakkındaki bilgi, tutum ve davranışlarını değerlendirmektir.

Gereç ve Yöntem: Bu kesitsel anket çalışması, Mayıs ve Temmuz 2019 tarihleri arasında İzmir, Türkiye'deki beş hastanede gerçekleştirildi. Veriler, 299 pediatri ve 126 OB/GYN asistanından çevrimiçi anket aracılığıyla elde edildi. İstatistiksel analizler SPSS® kullanılarak yapıldı.

Bulgular: Genel katılım oranı %72 idi. Asistanların sadece %25,2'si HPV aşısı hakkında yeterli bilgiye sahipti. OB/GYN asistanlarının bilgi puanları pediatri asistanlarına göre anlamlı derecede yüksekti (ortanca [IQR] = 9,4 [8,4-10,6] ve 8,4 [7,4-9,8], p=0,007). Asistanlar arasında aşılama oranı düşük olup, kadın asistanların aşılama oranı erkek asistanlara göre daha yüksekti (%13,6 ve %1,1, p<0,01). Asistanların %68,3'ü hem oğullarını hem de kızlarını aşılayacaklarını belirtirken, sadece %13,1'i hastalarına her zaman HPV aşısını tavsiye etmekteydi.

Sonuç: Çalışma, OB/GYN ve pediatri asistanlarının HPV aşısı hakkındaki bilgi ve aşılama oranlarının yetersiz olduğunu ortaya koymaktadır. Bu hekim gruplarına yönelik eğitim ve desteğin artırılması, HPV aşılama oranlarının iyileştirilmesi ve toplumda HPV ile ilişkili hastalıkların yaygınlığının azaltılması için önemlidir.

Anahtar Kelimeler: HPV aşısı; pediatrist; jinekolojist; asistan; bilgi; tutum ve davranış

1. Introduction

Cervical cancer is a prevalent form of cancer worldwide and ranks fourth among cancers affecting women (1). *Human papillomavirus* (HPV) is the leading risk factor for cervical cancer and is also linked to oropharyngeal, anal, vulvar, vaginal, and penile cancers. A total of 90% of cervical cancer cases are preventable, and screening and early diagnosis of cervical cancer results in a good prognosis (1-3). In Turkey, 1245 women deaths occur annually from cervical cancer, 67% of which are estimated to be associated with HPV 16-18 (4).

Significant reductions in the prevalence of HPV-16/18, anogenital warts, and HPV-related cancers have been observed with the HPV vaccine in both genders (5-8). The risk of cervical cancer is lower when individuals are vaccinated at an early age (9,10).

Since its licensing in the United States in 2006, the HPV vaccine has been available in more than 100 countries for both genders. It has been included in the vaccination schedule in numerous countries, including the Australia, Canada, France, Germany, Israel, and United States (11,12). In Turkey, the quadrivalent vaccine was licensed in 2007, and the bivalent vaccine was licensed in 2008. However, HPV vaccines are not included in the national vaccination program in Turkey.

Reviewing studies that assessed parents' attitudes toward HPV vaccination for their children, Trim et al. highlighted a decline in parents' awareness and intention to vaccinate their children, with safety concerns and the need for more information from doctors being key factors (13). Pediatric and obstetrics and gynecology (OB/GYN) specialists have a pivotal role in promoting this vaccine (13,14). Thus, a cross-sectional survey study was conducted to investigate the knowledge, attitudes, and practices of OB/GYN and pediatric residents about the HPV vaccine in Izmir, Turkey.

2. Methods

This cross-sectional survey study was conducted in five hospitals, including education, research, and medical faculty hospitals in Izmir, Turkey, between May and July 2019.

An online web-based survey was used as a data collection tool. In this study, a 16-question survey was created and conducted via Google Forms. The survey included questions pertaining to the respondents' demographic data, HPV vaccination status, knowledge about cervical cancer and the HPV vaccine, attitudes, and behavior regarding HPV vaccination (Appendix 1). The survey did not employ open-ended questions. The participants were selected through convenience sampling. The survey link was distributed to all residents (299 pediatric and 126 OB/GYN residents) in the research group via email. Informed consent was obtained from the participants before participating in the survey and it was stated that all answers would remain confidential. The survey was made available online for a period of one month, allowing respondents sufficient time to complete the survey. In order to ensure the anonymity and privacy of the participants, their personal online footprints were not collected. The respondents to the questionnaire were included in the study. A single questionnaire was permitted to be completed via a single email address.

A study conducted in our country revealed that the average knowledge score of all physicians was 20.28 (59.6%) in 34 questions (15). Similarly, in Turkey, another study of non-OB/

GYN physicians reported a mean score of 4.88±0.77 (81.3%) on 6 questions (16). Given the considerable variation in mean knowledge levels observed in other studies and the limited scope of our investigation, which was confined to OB/GYN and pediatric residents, we postulated that the average correct answer would fall within the range delineated by the two aforementioned studies in Turkey (17-21). Consequently, respondents who achieved a score of at least 10 correct answers (62.5%) on the 16 knowledge questions (15 five-point Likert scale questions and 1 multiple choice question) were deemed to possess an adequate level of knowledge regarding cervical cancer and the HPV vaccine. A total score was obtained by assigning values from one to five to the knowledge questions, which were scored according to a five-point Likert scale. The score was then divided by five to obtain the knowledge score, which was subsequently reported.

The data were uploaded into Microsoft Office Excel and then evaluated statistically using the Statistical Package for Social Sciences (SPSS®, version 23.0) software. The dataset was subjected to a process of analysis that excluded any responses that were missing values. The internal consistency of the survey was calculated and reported using the alpha method of Cronbach's alpha, intraclass correlation coefficient, the Hotelling's T-squared Test, and the Tukey nonadditive test. The normality of the data was evaluated using the Shapiro–Wilk test. The descriptive statistics of the continuous variables are presented in accordance with the normality criteria as the mean and standard deviation (SD) or median and interquartile range (IQR, 25th-75th percentile). The descriptive statistics for categorical variables were presented as numbers and percentages (n, %). The χ^2 test or Fisher's test was used for the comparison of categorical data. The Kruskal-Wallis H test or one-way ANOVA test was used to determine whether the knowledge score was significantly different between more than two independent groups. If a significant difference was found between the groups after the comparisons, the group or groups from which the difference originated were evaluated by post hoc analysis using Tukey's and Bonferroni tests. A p-value less than 0.05 was considered to indicate statistical significance.

The study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Dr. Behçet Uz Children's Hospital (2019/351) in accordance with the ethical standards established in the 1964 Declaration of Helsinki and its subsequent amendments.

The study was reported in accordance with the CROSS (A Consensus-Based Checklist for Reporting of Survey Studies) guidelines (Appendix 2) (22).

3. Results

Cronbach's alpha coefficient showed that the questionnaire achieved acceptable internal consistency (α=0.765; standardized α=0.697). Most questions seemed worthy of keeping in the survey, as they would result in a decrease in alpha if deleted (α=0.741-0.775). The only exception is the eleventh question, for which the alpha coefficient increased to 0.775 when it was removed from the questionnaire. Hotelling's T-Squared Test and Tukey's non-additive test were significant (F=77.453 and 85.411, respectively; both p<0.001).

The overall participation rate was 72% (83.6% for pediatric residents and 44.4% for OB/GYN residents). The median age of the participants was 28 (IQR:27-29) years. Most of the residents who participated in the study were women (69.6%). Eighty percent of the participants who completed the survey were pediatric residents. The descriptive characteristics of the participants are presented in Table 1.

Table 1. The descriptive characteristics of residents

Age (year), median (Q_1-Q_3)	28 (27-29)
Sex, n (%)	
Female	213 (69.6)
Male	93 (30.3)
Specialty, n (%)	
Pediatric	250 (81.6)
Gynecology & Obstetrics	56 (18.3)
Residency Duration, n (%)	
0-12 months	63 (20.5)
13-24 months	52 (16.9)
25-36 months	72 (23.5)
37-48 months	95 (31)
49 months and above	24 (7.8)
Marital Status, n (%)	
Married	105 (34.3)
Single	196 (64.0)
Divorced	5 (1.6)
Number of Children, n (%)	
None	261 (85.2)
1 child	35 (11.4)
2 children	10 (3.2)

Q_1-Q_3: 25th-75th percentile

Only 33% of the 306 residents who responded to the survey indicated that they knew enough about the HPV vaccine. More OB/GYN residents thought they had sufficient knowledge compared to pediatric residents (44.6% vs. 31.6%, *p*=0.04). The proportion of participants who considered themselves to have sufficient knowledge in self-assessment was higher among residents who had been in training for less than 24 months (*p*=0.03).

The median knowledge score was 8.6 (7.75-10.0). Only 25.2% (n=77) of the residents had sufficient knowledge about the HPV vaccine. The knowledge scores of the participants according to their demographic characteristics are presented in Table 2. The residents of OB/GYN had a significantly higher level of knowledge score than the pediatric residents (median (IQR)=9.4(8.4-10.6) and 8.4(7.4-9.8) respectively, *p*=0.007). The mean knowledge score of the residents who stated that they had sufficient knowledge about HPV was higher than those who stated that they did not have sufficient knowledge (*p*<0.001). There were no significant differences between the knowledge scores of residents based on age, marital status, child status, gender, or residency duration. Although residents with less than 24 months of training reported having more knowledge, there was no significant difference in knowledge scores between these residents and those with more than 25 months of training (*p*=0.71).

The false proposition "*HPV vaccine is only applied to sexually active women*" in the question about the HPV vaccine was marked as correct (*disagree* or *strongly disagree*) by female residents more than by male residents (58.7% and 38.7% respectively, $\chi^2(1)=10.4$, *p*=0.001, OR=2.25, 95% CI=1.36-3.70). Pediatric residents marked the false proposition that *"HPV vaccine may cause HPV infection"* significantly more correct (*disagree* or *strongly disagree*) compared to OB/GYN residents (62.8% and 41.1% respectively, $\chi^2(1)=11.1$, *p*=0.003, OR=2.42; 95% CI: 1.34-4.37). The rate of OB/GYN residents who found the proposition that lifelong protection can be achieved with HPV vaccination to be true was statistically significantly higher than that of pediatric residents (30.4% and 13.2% respectively, $\chi^2(1)=9.85$, *p*=0.002, OR= 2.87; 95% CI=1.46-5.64).

Table 2. The number of correct answers according to the descriptive characteristics of residents

	n	Number of correct answers, median (Q_1-Q_3)	p
Sex			
Male	93	8.4 (7.4-9.6)	0.074
Female	213	8.8 (7.8-10.2)	
Specialty			
Gynecology & Obstetrics	56	9.4 (8.4-10.6)	0.007
Pediatric	250	8.4 (7.4-9.8)	
Marital status			
Married	110	8.8 (7.8-10.0)	0.55
Single	196	8.6 (7.6-9.8)	
Residency duration			
Less than 24 months	115	8.4 (7.4-10.2)	0.71
More than 25 months	191	8.6 (7.8-9.8)	
Knowledge level about HPV			
I know	104	10.5 (9.0-11.2)	<0.001
I do not know	202	8.4 (7.4-9.6)	
Child Status			
No child	261	8.6 (7.6-9.8)	0.45
Having children	45	8.8 (8.0-10.4)	

HPV: Human papillomavirus, Q_1-Q_3: 25th-75th percentile.
*Bold values indicate statistical significance at the p<0.05 level

The vaccination rate of female residents was 13.6%. Only one male resident (1.1%) reported HPV vaccination. Female residents had significantly higher HPV vaccination rates than male residents (p<0.01). The HPV vaccination rates of residents were not significantly different according to their specialty (p=0.07).

Among residents, 7.1% indicated that they would only vaccinate their daughters against HPV, while 68.3% stated that they would vaccinate both their sons and daughters against HPV. It was observed that 31.5% of male and 16% of female residents chose the option "*I do not want to have my children vaccinated against HPV*". On the other hand, 58.7% of male and 72.8% of female residents chose the option "*I would get both my daughter and my son vaccinated*". A significant difference was found between the residents' opinions about vaccinating their children according to gender (p=0.01).

Those who did not intend to vaccinate their children were asked to provide their reasons. Most of those who did not intend to vaccinate their son (55.2%) believed the vaccine was unnecessary. In contrast, the majority of those who did not intend to vaccinate their daughter (55.5%) stated that they lacked sufficient information about the vaccine. The proportion of respondents who cited high cost as a reason for not vaccinating their daughters was 6.9%, whereas the corresponding figure for sons was 3.5%.

When queried about their recommendations for HPV vaccination, 13.1% (n=40) of the residents indicated that they would always recommend it, 29.7% (n=91) that they would often recommend it, 18.6% (n=57) that they would sometimes recommend it, 30.4% (n=93) that they would rarely recommend it, and 8.2% (n=25) that they would never recommend it. There were no statistically significant differences between gender, specialty, duration of residency, age, marital status, having children, or having had their children vaccinated in terms of recommending HPV vaccination to their patients.

The vaccination recommendations and knowledge scores of residents are presented in Table 3. When the residents were grouped according to the status of recommending vaccination to their patients, there was no significant difference between the groups in terms of the median knowledge score (H(4, n=301) = 8.88, p=0.069). When residents were grouped according to the vaccination (or considered vaccination) status of their children, a significant difference was observed between the groups in terms of knowledge score (H(3, n=301) = 8.45, p=0.034). A post hoc analysis revealed that the median knowledge score of individuals who selected "both" was statistically significantly higher than that of those who selected "only daughter" (n 209 and 22; median (IQR) 8.8 (7.8-10.2) and 7.8 (7.0-9.0), respectively; p=0.039).

The vaccine recommendations grouped by specialty and knowledge score are shown in Figure 1. No statistically significant correlation was identified between vaccination recommendation and specialty (χ^2(3)=4.15, p=0.246; χ^2(4)=4.33, p=0.363; respectively).

The proportion of residents who thought that the HPV vaccine should be included in the national vaccination schedule was 50.6%, and 96.7% of the residents who participated in the study stated that they wanted to receive information about the HPV vaccine.

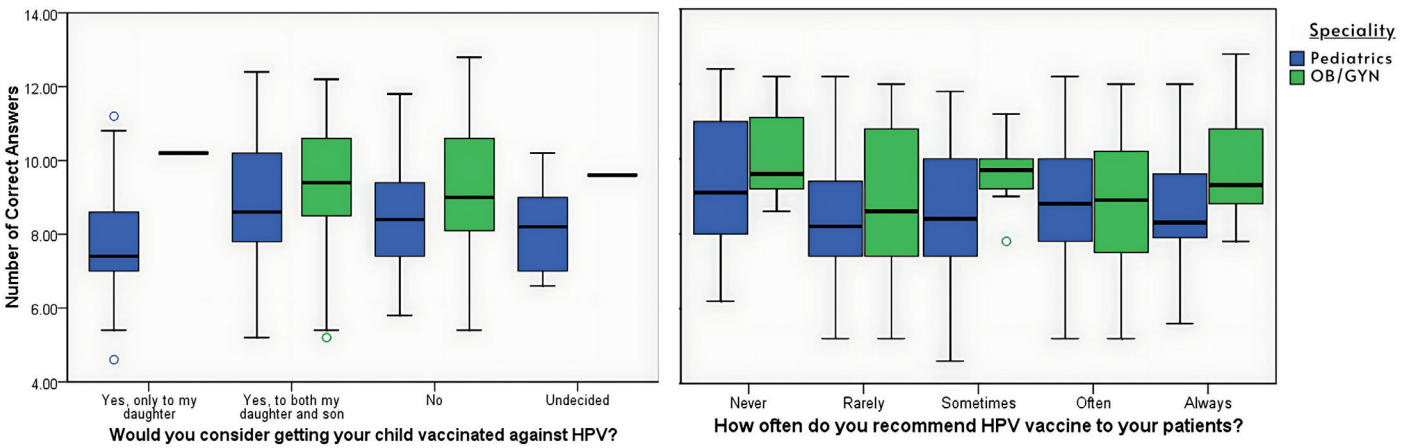

Figure 1. Vaccination recommendations and the number of correct answers by residents grouped according to their areas of specialty
G&O: Gynecology & obstetrics, HPV: Human Papillomavirus
In the box plot, the lower end of the black box represents the 25th quartile, the upper end represents the 75th quartile, the length represents the interquartile range (IQR), the length of the line extending outside the box represents the range, and the black line inside the box represents the median.

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Table 3. Vaccination recommendations and numbers of correct answer of residents

Would you consider getting your child vaccinated against HPV?			How often do you recommend HPV vaccine to your patients?					
			Never	Rarely	Sometimes	Often	Always	Total
Yes, only to my daughter		n	2	4	5	7	4	22
		Row %	9.1%	18.2%	22.7%	31.8%	18.2%	100.0%
		Column %	8.0%	4.3%	8.8%	7.7%	10.3%	7.2%
	NCA	Median	8.50	7.30	6.60	8.20	8.40	7.80
		Q1	6.20	6.30	6.00	7.40	7.70	7.00
		Q3	10.80	8.20	7.20	9.60	9.00	9.00
		IQR	4.6	1.9	1.2	2.5	2.7	2.0
Yes, to both my daughter and son		n	20	68	35	64	22	209
		Row %	9.6%	32.5%	16.7%	30.6%	10.5%	100.0%
		Column %	80.0%	73.1%	61.4%	70.3%	56.4%	68.5%
	NCA	Median	9.40	8.30	9.40	8.90	8.70	8.80
		Q1	8.90	7.40	8.00	7.80	8.00	7.80
		Q3	11.20	9.50	10.40	10.50	10.20	10.20
		IQR	2.3	1.9	2.4	2.7	2.2	2.4
No		n	3	17	13	19	11	63
		Row %	4.8%	27.0%	20.6%	30.2%	17.5%	100.0%
		Column %	12.0%	18.3%	22.8%	20.9%	28.2%	20.7%
	NCA	Median	8.40	9.00	7.80	9.00	8.40	8.60
		Q1	8.00	8.00	7.40	7.00	7.40	7.40
		Q3	8.80	10.00	8.60	9.80	9.80	9.40
		IQR	0.8	2	1.2	2.8	2.4	2.0
Undecided		n	0	4	4	1	2	11
		Row %	0.0%	36.4%	36.4%	9.1%	18.2%	100.0%
		Column %	0.0%	4.3%	7.0%	1.1%	5.1%	3.6%
	NCA	Median	.	7.20	8.30	8.40	9.70	8.40
		Q1	.	6.80	7.30	8.40	9.20	7.00
		Q3	.	8.20	9.10	8.40	10.20	9.20
		IQR	-	1.4	1.8	0.0	2	2.2
Total		n	25	93	57	91	39	305
		Row %	8.2%	30.5%	18.7%	29.8%	12.8%	100.0%
		Column %	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
	NCA	Median	9.40	8.40	8.60	8.80	8.60	8.60
		Q1	8.60	7.40	7.40	7.80	8.00	7.80
		Q3	11.00	9.40	10.00	10.20	9.80	10.00
		IQR	2.4	2	2.6	2.4	1.8	2.2

HPV: Human Papillomavirus, NCA: Number of Correct Answers, IQR: Interquartile range, Q_1: 25th percentile, Q_3: 75th percentile.

4. Discussion

This study aimed to assess the knowledge, attitudes, and practices of OB/GYN and pediatric residents in Izmir, Turkey, regarding the HPV vaccine. The main findings of the study were as follows: Only 25.2% of residents had adequate knowledge about HPV and HPV vaccine, residents had unexpectedly low vaccination rates, and only 13.1% of residents always recommended HPV vaccine to their patients. The findings indicate that these physician groups, which play a pivotal role in disseminating information and guidance to the community, should receive enhanced training and support in the dissemination of the HPV vaccine, given that it is not included in the national vaccination program in Turkey.

The results of the study are in accordance with the findings of previous studies. For instance, numerous studies have demonstrated that health workers' knowledge of HPV infection and HPV vaccination is insufficient (17-19,21,23-26). However, in contrast to these studies, Mexican doctors' knowledge of cervical cancer was reported to be adequate (27). A study conducted in Turkey revealed that the average HPV knowledge level of non-OB/GYN physicians was adequate (16). These differences may be attributed to variations in health policies, educational systems, and cultural norms between countries.

It is notable that the vaccination rates of residents were low, which is similar to other studies in the literature. In a study by Özçam et al. it was found that the vaccination rate among female health workers was 6.5% (28). This can be explained by factors such as the cost of the vaccine, reliability concerns, and potential impact on sexual practices (29-32). Furthermore, these low rates are inadequate in light of the vaccine's protective efficacy.

The proportion of residents who had received or were considering HPV vaccination for their children was consistent with those reported in the existing literature. The high rate of pediatricians vaccinating their daughters was consistent with the findings of the study by Ozsurekci et al. (33). Similarly, Tolunay et al. reported that pediatricians and obstetricians had high rates of vaccination of their girls (14). In one study, physicians in Malaysia recommended vaccination for only 26.3% of boys (34). Similarly, Tolunay et al. reported that 79.5% of pediatricians and obstetricians/gynecologists preferred to vaccinate girls, while 36.7% preferred to vaccinate boys (14). In a separate study conducted in Turkey, 52.7% of non-OB/GYN physicians indicated approval for vaccination for themselves, 84.3% for their daughters, and 56.8% for their sons (16). This study found that the rates of residents who had or were considering HPV vaccinations for their children were consistent with the literature. However, although the proportion of residents who would consider vaccinating their children was high, the proportion of those who vaccinated themselves was low. This finding indicated that there was a clear inconsistency between the health practices of health workers and their professional advice, which requires further investigation.

A previous study revealed that general practitioners/family doctors who did not vaccinate their daughters against HPV were 20% less likely to recommend HPV vaccination to their patients (35). In another study conducted among health workers, it was found that the most common reasons for not vaccinating girls were the safety of the vaccine (41.2%), the cost of the vaccine (10%) and the increased freedom of sexual intercourse after vaccination (5%) (29). A previous study reported that gynecologists demonstrated a high level of knowledge regarding vaccination, yet they cited financial concerns and patient refusal as significant barriers to its implementation (30). In their study, Yıldırım et al. found that cost was the most frequently cited reason by pediatricians for not recommending vaccination (31). In another study conducted in Turkey, the high cost of the HPV vaccine was cited by 50 percent as the reason for not getting the vaccine (32). These findings indicate that cost and concerns about the safety of the HPV vaccine have a considerable influence on health professionals and families regarding the dissemination of HPV vaccination.

The low rate of residents who recommended HPV vaccination to their patients was similar to that reported in another study conducted in Turkey (36). In the same study, it was reported that 29.6% of family physicians and 36.6% of pediatricians provided information about adolescent vaccines, including HPV vaccinations if the adolescent or the adolescent's family requested such information. This may be attributed to a lack of knowledge among physicians regarding the subject of vaccination.

It has been demonstrated that patients' inclination toward vaccination is contingent on the extent of knowledge that physicians possess regarding vaccines (37). Similarly, Rosen et al. obtained similar results in terms of participants' level of knowledge. The study also emphasized that the opportunities offered by the HPV vaccine should be utilized and the level of knowledge of physicians about this vaccine should be increased (20).

The findings of this study highlight the necessity to address the deficiency in knowledge regarding HPV vaccination among OB/GYN and pediatric residents. Eliminating this deficiency may increase vaccination rates in the community and reduce diseases associated with HPV infection (38). In addition, as in

many countries, it is necessary to identify barriers to the HPV vaccine in Turkey and develop strategies to increase vaccine coverage (39).

Strengths and limitations

This study was conducted only with pediatric and OB/GYN residents in Izmir and is not generalizable nationally. Therefore, a multicenter national study is needed. The reasons for non-participation among residents who declined to participate in the study were not evaluated. Although the internal consistency of the questionnaire was appropriate, a pre-test questionnaire would be preferable. Residents were asked whether they intended to have their children vaccinated against HPV. However, the question should have been phrased in a way that distinguished between the rates at which they had been vaccinated and at which they planned to vaccinate.

This study is one of a limited number of available studies that report on the attitudes, practices, and knowledge levels of pediatric and OB/GYN residents regarding HPV and the HPV vaccine. As a result, this study may inform the clinical approach of physicians, residency training, and future studies on this subject.

As a result, the findings of this study offer valuable insights that can inform the dissemination of the HPV vaccine. It also underscores the necessity for enhanced educational and support initiatives to augment the knowledge of pediatric and obstetrics/gynecology residents in Turkey regarding HPV vaccines. This may increase vaccination rates within the community, thereby contributing to a reduction in HPV infection and the diseases that are a consequence of it.

Acknowledgments

The authors thank all the participating healthcare providers from Tepecik Training and Research Hospital, Dr. Behçet Uz Pediatrics and Surgery Training and Research Hospital, Ege University, Dokuz Eylül University, and İzmir Katip Çelebi University.

Declaration of AI and AI-assisted technologies in the writing process

In the course of composing the article, the DeepL Translator & Write and PoolText were employed for the purposes of spelling, grammar, and reference accuracy. After using this tools/services, the authors reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Author contribution

Study conception and design: NE and İG; data collection: NE and DO; analysis and interpretation of results: NE, DO, AE, and İG; draft manuscript preparation: NE, DO, AE, and İG. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee (Protocol no. 06/02.01.2020).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

Yazar katkısı

Araştırma fikri ve tasarımı: NE ve İG; veri toplama: NE ve DO; sonuçların analizi ve yorumlanması: NE, DO, AE, ve İG; araştırma metnini hazırlama: NE, DO, AE, ve İG . Tüm yazarlar araştırma sonuçlarını gözden geçirdi ve araştırmanın son halini onayladı.

Etik kurul onayı

Bu araştırma için Dr. Behçet Uz Çocuk Hastalıkları ve Cerrahisi Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulundan onay alınmıştır (Karar no: 06/02.01.2020).

Finansal destek

Yazarlar araştırma için finansal bir destek almadıklarını beyan etmiştir.

Çıkar çatışması

Yazarlar herhangi bir çıkar çatışması olmadığını beyan etmiştir.

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Türk Kadın Sağlığı ve Neonatoloji Dergisi

To cite this article: Yıldırım M, Altınsoy H, Ünlübilgin E, Engin-Üstün Y. The role of peripheral blood inflammation ındices in patients with a diagnosis of endometrial hyperplasia and cancer. Turk J Womens Health Neonatol 2024; 6(4): 147-152.

Orijinal Makale

The Role of Peripheral Blood Inflammation Indices in Patients with a Diagnosis of Endometrial Hyperplasia and Cancer

Endometrial Hiperplazi ve Kanser Tanılı Hastalarda Periferik Kan İnflamasyon İndekslerinin Rolü

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Abstract

Purpose: Endometrial cancer (EC) is an important problem with its increasing incidence, especially in developed countries. There is no generally accepted screening program yet. The management of endometrial hyperplasia (EH), which is the most important risk factor, is complex because it is an invasive process.

Methods: A retrospective study was conducted with a total of 72 patients. Patients between the ages of 35-65 with abnormal uterine bleeding, and increased endometrial thickness on transvaginal sonography were evaluated with pathology results. Sociodemographic characteristics of the patients and laboratory values at hospital admission were obtained from hospital records. White blood cells (WBC), neutrophils, lymphocytes, monocytes, eosinophils, basophils, and thrombocyte counts ($x10^9$/L); plateletcrit (%), hemoglobin (Hb) (g/dL), and hematocrit (Htc) (%) values were recorded. Neutrophil lymphocyte ratio (NLR), monocyte lymphocyte ratio (MLR), and thrombocyte lymphocyte ratio (TLR) were obtained. Systemic immune-inflammation index (SII), systemic inflammation response index (SIRI) and pan-immune-inflammation value (PIV) were obtained.

Results: Thirty-seven patients diagnosed with EH and 35 patients diagnosed with endometrial malignancy were included. The mean age of the EH was 45.5 years and the mean age of the malignant group was 50.5 years (p=0.027). The sociodemographic characteristics of the patients were found to be similar. There was no significant difference in complete blood count parameters between two groups. Mean values of NLR were 2.33 and 2.52 in EH and EC groups, respectively, p = 0.448. Mean values of MLR were 0.20 and 0.21, respectively, p = 0.498. Mean values of TLR were 0.16 and 0.15, respectively, p = 0.811. Mean values of SII were 720.1 and 812.4 ($x10^9$/L), respectively, p = 0.456. Mean values of SIRI were 943.1 and 1095.6 ($x10^9$/L), respectively, p = 0.257. Mean values of PIV were 312753.6 and 352975.1 ($x10^9$/L), respectively, p = 0.514.

Conclusion: Peripheral blood inflammation indices have recently been used in cancer diagnosis and follow-up. We did not find any statistically significant differences in the investigated parametrers between the EH and EC patient groups. Close follow-up is necessary in the presence of additional risk factors in women with EH.

Keywords: endometrial cancer; endometrial hyperplasia; systemic immune-inflammation index; systemic inflammation response index; pan-immune-inflammation value

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DOI: 10.46969/EZH.1572727
Geliş tarihi: 23.10.2024 Kabul tarihi: 04.11.2024

Volume 6 Number 4 p: 147-152

Öz

Amaç: Endometrium kanseri (EK) , özellikle gelişmiş ülkelerde artan sıklığıyla önemli bir sorundur. Henüz genel kabul görmüş bir tarama programı yoktur. En önemli risk faktörü olan endometrial hiperplazinin (EH) yönetimi, invaziv bir süreç olması nedeniyle karmaşıktır.

Gereç ve Yöntem: Toplam 72 hasta ile retrospektif bir çalışma yürütüldü. Anormal uterin kanaması ve transvajinal sonografide artmış endometrial kalınlığı olan 35-65 yaş arasındaki hastalar patoloji sonuçlarıyla değerlendirildi. Hastaların sosyodemografik özellikleri ve hastane yatışındaki laboratuvar değerleri hastane kayıtlarından elde edildi. Beyaz kan hücreleri (WBC), nötrofiller, lenfositler, monositler, eozinofiller, bazofiller ve trombosit sayıları (x10^9/L); plateletcrit (%), hemoglobin (Hb) (g/dL) ve hematokrit (Htc) (%) değerleri kaydedildi. Nötrofil lenfosit oranı (NLO), monosit lenfosit oranı (MLO) ve trombosit lenfosit oranı (TLO) elde edildi. Sistemik immün-inflamasyon indeksi (SII), sistemik inflamasyon yanıt indeksi (SIRI) ve pan-immün-inflamasyon değeri (PIV) elde edildi. Verilerin dağılımı SPSS ile programı ile analiz edildi. Parametrik veriler bağımsız örneklem t-testi ile incelendi. 0,05'ten küçük p değeri anlamlı kabul edildi.

Bulgular: EH tanısı almış 37 hasta ve endometrial malignite tanısı almış 35 hasta çalışmaya dahil edildi. EH grubunun yaş ortalaması 45,5 yıl iken malign grubun yaş ortalaması 50,5 yıl idi (p=0,027). Hastaların sosyodemografik özellikleri benzer bulundu. Tam kan sayımı parametrelerinde iki grup arasında istatistiksel olarak anlamlı fark yoktu. Sistemik inflamatuar indeksler gruplar arasında karşılaştırıldı. EH ve EK gruplarında ortalama NLR değerleri sırasıyla 2,33 ve 2,52 idi, p=0,448. MLO ortalama değerleri sırasıyla 0,20 ve 0,21 idi, p=0,498. TLO ortalama değerleri sırasıyla 0,16 ve 0,15 idi, p=0,811. SII ortalama değerleri sırasıyla 720,1 ve 812,4 (x10^9/L) idi, p=0,456. SIRI'nin ortalama değerleri sırasıyla 943,1 ve 1095,6 (x10^9/L) idi, p = 0,257. PIV'nin ortalama değerleri sırasıyla 312753,6 ve 352975,1 (x10^9/L) idi, p = 0,514.

Sonuç: Periferik kan inflamasyon indeksleri son zamanlarda kanser tanısı ve takibinde kullanılmaktadır. EH ve EK hasta grupları arasında araştırılan parametreler arasında istatistiksel olarak herhangi bir anlamlı fark bulamadık. EH'li kadınlarda ek risk faktörlerinin varlığında yakın takip gereklidir.

Anahtar Kelimeler: endometrial kanser; endometrial hiperplazi; sistemik immün-inflamasyon indeksi; sistemik inflamasyon yanıt indeksi; pan-immün-inflamasyon değeri

1. Introduction

Endometrial cancer (EC) is the second most common gynaecologic cancer and the fourth leading cause of cancer death worldwide (1). The incidence of this disease is increasing rapidly and has become more common in the developed world over the last few decades (2). Previously known as a post-menopausal disease, its incidence in women under 50 has increased in recent years (3). Obesity, metabolic syndrome, advanced age, nulliparity, infertility, unopposed estrogen exposure, diabetes mellitus are some risk factors. Vaginal bleeding is the most common symptom and usually causes symptoms. Therefore, early diagnosis and correct treatment of precancerous lesions is essential for management. The gold standard for diagnosis is endometrial sampling and histopathological examination. There is currently no well-established screening method for EC, except for the recommendation of annual endometrial sampling from the age of 35 for those with a family history of cancer (4). Endometrial hyperplasia (EH) is a common gynaecological endocrine pathology characterised by an increase in the ratio of endometrial glands to strom, as opposed to the normal proliferative endometrium. It's main clinical significance is that it is a known precursor lesion of the endometrioid type, the most common type of EC (5). The differentiation and transition between low- risk and high- risk EH is recognized to be continuous (6). Risk factors include diabetes, advanced age and increased body mass index (BMI) (7). Exposure to unopposed estrogen stimulation is the best identified mechanism of hyperplasia. Early diagnosis and treatment are very valuable for patients with precancerous lesions (8).

Inflammation and the excessive release of pro-inflammatory cytokines in the microenvironment of cancer tissue affect bone marrow cell production. Thus, defects in the immune response mechanism promote cancer development and progression. There is increasing evidence for the use of peripheral blood parameters as alternative markers reflecting the inflammatory status in cancer (9,10). Higher systemic inflammation response index (SIRI) levels were associated with the efficacy of neoadjuvant chemotherapy in breast cancer (11). Pan-immune-inflammation value (PIV) was found to predict recurrence in patients with left-sided colon cancer (12). Histopathological examination is the gold standard for diagnosing endometrial pathology, but systemic inflammatory markers are used clinically as an adjuct to demonstrate tumour aggressiveness and invasiveness. Systemic immune-inflammation index (SII) is a marker that has been evaluated between early and advanced stages of EC (13).

We hypothesised that malignant endometrial pathologies are associated with systemic inflammation, and our primary aim is to compare peripheral blood parameters in EH and cancer.

2. Materials and Methods

Study Population

The retrospective study was conducted on 72 patients who underwent endometrial biopsy and hysteroscopy at Etlik Zübeyde Hanım Women's Gynaecology Training and Research Hospital between 1 January 2024, and 1 September 2024. The study was approved by the institution's education planning committee with decision number 23.08.2024-08/07.

Patients aged of 35-65 years with abnormal uterine bleeding, and increased endometrial thickness on transvaginal sonography were evaluated with pathology results. Those with inflammatory, hematological, rheumatological, thyroid diseases, hyperprolactinemia, steroid and tamoxifen use, and hormone replacement therapy, those diagnosed with secretory, proliferative endometrium, endometrial intraepithelial neoplasia (EIN) as a result of histopathological examination were excluded. The patient's sociodemographic characteristics, preoperative laboratory, and pathology results were obtained from hospital records. White blood cell (WBC), neutrophil, lymphocyte, monocyte, eosinophil, basophil, and thrombocyte counts (x10^9/L), plateletcrit (%), hemoglobin (Hb) (g/dL), and hematocrit (Htc) (%) values were recorded before the intervention. Neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and thrombocyte-lymphocyte ratio (TLR) were calculated. The SII was obtained by dividing the product of neutrophil and thrombocyte counts by the lymphocyte count (x10^9/L); the SIRI was calculated by dividing the product of neutrophil and monocyte numbers by the lymphocyte count (x10^9/L); PIV was calculated by dividing the product of neutrophil, monocyte, and thrombocyte counts by the lymphocyte counts (x10^9/L).

Statistical analysis

The IBM Statistical Package for the Social Sciences software version 25.0; SPSS Inc., Armonk, NY was used for data analysis. The Kolmogorov-Smirnov test was used to examine the distribution of the data. Descriptive statistics were presented as mean ± standard deviation for normally distributed data. Parametric data were compared using the independent sample t-test.

3. Results

A total of 72 patients were enrolled in the study. Thirty-seven participants diagnosed with EH and 35 participants diagnosis with malignancy based on endometrial biopsy and operative hysteroscopy results were included in the study. The mean age of the EH group was 45.5 years and the mean age of the malignant group was 50.5 years (p=0.027). The socio-demographic characteristics of the patients were similar (Table 1).

Complete blood count parameters were compared (Table 2). The mean WBC counts were 7.172 and 7.808 (x10^9/L) respectively, p=0.205. Mean neutrophil counts were 4.530 and 5.059 (x10^9/L) respectively, p=0.208. The mean lymphocyte counts were 2.078 and 2.116 (x10^9/L) respectively, p=0.787. The mean monocyte counts were 0.404 and 0.441 (x10^9/L), respectively, p= 0.331. The mean eosinophil counts were 0.114 and 0.157 (x10^9/L), p= 0.158. The mean basophil counts were 0.031 and 0.041 (x10^9/L), respectively, p= 0.080. The mean thrombocyte counts were 309 and 301 (x10^9/L), respectively, p= 0.770. The mean PCT counts were 0.31 and 0.30 (%), respectively, p= 0.643. The mean Hb values were 11.9 and 11.9 (g/dL) respectively, p= 0.857. The mean Hct values were 36.4 and 37.1 (%), respectively, p= 0.582.

The indices were the compared between groups (Table 3). The mean values of NLR were 2.33 and 2.52 in the premalignant and malignant groups, respectively, p= 0.448. The mean values of MLR were 0.20 and 0.21, respectively, p= 0.498. The mean

Table 1. Comparison of sociodemographic features of hyperplasia and cancer groups

	EH (n=37)	EC (n=35)	p-value
Age (years)	45.5±6.8	50.5±11.1	**.027***
BMI (kg/m^2)	26.2±3.8	27.3±3.4	.724
Gravidity (n)	3±1	3±2	.866*
Parity (n)	3±1	2±1	.395*
Abortus	0±0	1±0	.344*

*Comparison between groups was made with independent t test. Values are given as mean±standard deviation.
EH: endometrial hyperplasia, EC: endometrial cancer, BMI: body-mass index

Table 2. Comparison of laboratory data of the groups			
	EH (n=37)	**EC (n=35)**	**p-value**
WBC (x10^9/L)	7.172±2.067	7.808±2.155	.205*
Neutrophil (x10^9/L)	4.530±1.597	5.059±1.930	.208*
Lymphocyte (x10^9/L)	2.078±0.659	2.116±0.524	.787*
Monocyte (x10^9/L)	0.404±0.169	0.441±0.151	.331*
Eosinophile	0.114±0.077	0.157±0.086	.158*
Basophile	0.031±0.015	0.041±0.020	.080*
Thrombocyte (x10^9/L)	309±91	301±99	.770*
PCT (%)	0.31±0.09	0.30±0.08	.643*
Hb (g/dL)	11.9±2.3	11.9±2.2	.857*
Hct (%)	36.4±5.9	37.1±5.7	.582*
* Comparison between groups was made with independent t test. Values are given as mean±standard deviation. EH: endometrial hyperplasia, EC: endometrial cancer, PCT: plateletcrit			

Table 3. Comparison of peripheral blood inflammation indexes between groups			
	EH (n=37)	**EC (n=35)**	**p-value**
NLR	2.33±1.01	2.52±1.15	.448*
MLR	0.20±0.06	0.21±0.06	.498*
TLR	0.16±0.05	0.15±0.08	.811*
SII (x10^9/L)	720.1±374.5	812.4±641.7	.456*
SIRI (x10^9/L)	943.1±524.1	1095.6±607.1	.257*
PIV (x10^9/L)	312753.6±245588.2	352975.1±274447.9	.514*
* Comparison between groups was made with independent t test. Values are given as mean±standard deviation. EH: endometrial hyperplasia, EC: endometrial cancer			

values of TLR were 0.16 and 0.15, respectively, p= 0.811. The mean values of SII were 720.1 and 812.4 (x10^9/L), respectively, p= 0.456. The mean values of SIRI were 943.1 and 1095.6 (x10^9/L), respectively, p= 0.257. The mean values of PIV were 312753.6 and 352975.1 (x10^9/L), respectively, p= 0.514.

4. Discussion

The presented study investigated the role of inflammatory markers in predicting malignancy in patients with abnormal endometrial findings. The mean age of the EC group was shown to be higher than that of the EH group. Peripheral complete blood count indices showed no difference between hyperplasia and malignant endometrial pathology.

Several pro-inflammatory mediators are released in the tumour milieu, causing impairment of host immunity (14). Oxidative stress leads to haematological changes with the secretion of cytokines, chemokines and various enzymes. The most common are leukocytosis, neutrophilia and lymphopenia. When immunity is suppressed, an increase in the neutrophil-to- lymphocyte ratio is expected. Markers of the systemic inflammatory response have been investigated for diagnosing, prognosis, and predicting metastasis in various types of cancer (9,10,14). In distinction to other cancers, markers that can be used in diagnosis and prognosis will play a valuable role due to the genetic polymorphism and specific molecular structure of EC (15). In a previous study, NLR and TLR were found to be valuable in predicting lymph node metastasis in endometrial adenocarcinoma, but less effective than CA 125 (16). In another study, NLR was found to predict survival in epithelial ovarian cancer (17). In a review investigating the short and long-term prognostic value of SII in EC, increased SII was found to be associated with shorter survival (18). In the present study, the mean SII was found to be similar to the EH group. In a different study, SII was associated with adverse clinicopathological

features but not with recurrence-free survival (19). In the present study, no change in systemic inflammation markers were found in EC cases compared to EH cases. The early stage cancers in the EC group or the possibility of concurrent malignancy in the EH group may play a role in these results.

Although premalignant lesions of the endometrium have been included in various classifications in the past, they are now grouped under two main headings as benign EH and EIN. These two groups differ in their malignant potential, with EINs showing monoclonal growth and being true neoplasms, whereas benign EHs are polyclonal endometrium that develop in response to anovulation and an abnormal hormonal environment. Benign EH that develops due to unopposed estrogen exposure is at risk of EC as the duration of exposure increases (20). It is most common in perimenopausal women, as in this study. It can also be seen in young women with anovulatory cycles. Treatment is medical or surgical, depending on the patient's age, whether hyperplasia is present with or without atypia, and the patient's desire to have children. Hysterectomy is recommended for women with atypical hyperplasia and for women with persistent non-atypical hyperplasia because of the risk of concurrent or future EC if fertility is not desired. Accurate assessment of EC risk plays an important role in optimal clinical management.

The current study showed that women diagnosed with EC were older than those diagnosed with EH. This finding is consistent with studies in the literature. In a study comparing complete blood count parameters in 416 patients, the average age of the EC group was higher than that of the EH group (21). In another study examining platelet indices, the EC group was found to be older (22). Data show that the risk is higher after the age of 60 and that survival decreases (23). This may be due to reduced immune function in the postmenopausal period. Most of the estrogen in the postmenopausal female circulation is formed by peripheral aromatisation (23). The aromatising capacity of adipose tissue is stimulated by pro-inflammatory cytokines. Therefore, older age and obesity are risk factors for EC. In this study, BMI was similar between the groups. Contrary to our results, another study in the literature found that BMI was higher in the EC group (8). According to this study, the risk of EC was higher in EH patients with a BMI above 25 kg/m². In fact, there are recent data suggesting that weight loss prevents EC by reducing systemic inflammation and boosting immunity (24). In adition, nulliparity is also a known as a risk factor for EC. In our presented study, obstetric characteristics were similar between the two groups. Although there is no known screening method for EC, women with established risk factors, such as obesity, advanced age, hyperplasia, diabetes mellitus, and hypertension, may be subjected to closer clinical follow-up.

The strengths of the study are that the SIRI and PIV markers, which have not been previously studied in the EC and EH, were investigated. There are some limitations to our study. The retrospective nature of the research, a single preoperative blood sample, a relatively small number of patients, and the lack of postoperative pathological confirmation of those who underwent hysterectomy are some of the limitations. Studies including EC stages and prognostic markers can be planned.

5. Conclusion

In gynaecology practice, ultrasound and pathological examination are the gold standard for diagnosis. The significance of peripheral blood count parameters in benign, premalignant, and malignant endometrial pathologies is not clearly understood. The importance of early diagnosis has been enhanced by the increasing frequency of EC and the decreasing age of onset. In the presence of a diagnosis of EH, the risk of EC should be accurately assessed and shared decision-making strategies should be developed for patient management.

Author contribution

Study conception and design: MY, HA, EÜ, and YEÜ; data collection: MY, HA, EÜ, and YEÜ; analysis and interpretation of results: MY, HA, EÜ, and YEÜ; draft manuscript preparation: MY, HA, EÜ, and YEÜ. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Etlik Zubeyde Hanim Women's Health Education and Research Hospital (Protocol no. 08/23.08.2024).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

Yazar katkısı

Araştırma fikri ve tasarımı: MY, HA, EÜ ve YEÜ; veri toplama: MY, HA, EÜ ve YEÜ; sonuçların analizi ve yorumlanması: MY, HA, EÜ ve YEÜ; araştırma metnini hazırlama: MY, HA, EÜ ve YEÜ. Tüm yazarlar araştırma sonuçlarını gözden geçirdi ve araştırmanın son halini onayladı.

Etik kurul onayı

Bu araştırma için Etlik Zübeyde Hanım Kadın Hastalıkları Eğitim ve Araştırma Hastanesi Etik Kurulundan onay alınmıştır (Karar no: 08/23.08.2024).

Finansal destek

Yazarlar araştırma için finansal bir destek almadıklarını beyan etmiştir.

Çıkar çatışması

Yazarlar herhangi bir çıkar çatışması olmadığını beyan etmiştir.

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